PROTRACTED DEVELOPMENT OF BRAIN SYSTEMS UNDERLYING WORKING MEMORY IN ADOLESCENCE: A LONGITUDINAL STUDY

by

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Daniel J. Simmonds, PhD

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Working memory (WM), the ability to hold information on line to guide planned behavior, continues to improve through adolescence in parallel with brain maturational processes of systems known to support it. Initial studies have only examined individuals once or twice, limiting our understanding of developmental trajectories, leading to sparse and conflicting results. Further, it is unclear how age-related changes in WM performance and neural processes are associated, and what mechanisms might underlie these changes. In this study, we report on developmental improvements of WM performance and changes in brain function and connectivity of systems underlying WM using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), in a large longitudinal sample in which participants were followed annually for up to nine years. First, results confirmed that WM performance continues to improve into the early 20's. Alongside these refinements, brain activity in the frontal eye fields (FEF) and parietal cortex continue to change during this time; age-related changes in prefrontal regions were specifically associated with WM performance, suggesting a primary role in WM improvements. Supporting these changes, task-related functional connectivity from dorsolateral prefrontal cortex (DLPFC) to FEF, visual association cortex (VAC), and cingulate regions continued to change during adolescence and were related to WM development. Greater connectivity was associated with less mature behavior, suggesting a decreased reliance on top-down communication to support WM with development. DTI results indicated robust increases in white matter integrity across the brain with the several tracts connecting prefrontal and posterior systems, continuing to mature

into early adulthood. Further, white matter measures were correlated with behavior, functional activity, and functional connectivity, suggesting that the development of structural connections may provide a scaffold on which cognitive and functional brain development can specialize. Taken together, these results suggest that while regional prefrontal function supports the transition from childhood to adolescence, the period of transition to adult level WM performance is characterized, by enhancements in prefrontal functional and structural connectivity to posterior regions supporting mnemonic aspects of working memory residing in attention and visual association regions.

Keywords: dorsolateral prefrontal cortex, frontal eye fields, visual association cortex, cingulate, executive, sensorimotor, cognitive, maturation, timing, stages, epochs, functional magnetic resonance imaging, functional connectivity, beta series, diffusion tensor imaging, individual differences, brain-behavior, structure-function.

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PREFACE

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1.0 INTRODUCTION

1.1 ADOLESCENCE AND WORKING MEMORY

Adolescence is a critical period of the lifespan that supports the transition to mature adult level behavior. It is defined by the onset of puberty typically ranging from 10 to 12 years of age and concluding by 18 years of age [Dahl, 2004, Sisk and Zehr, 2005] or later through the early twenties [Arnett, 2000]. Adolescence is characterized by increases in sensation seeking that can lead to risk taking increasing mortality rates [Chambers et al., 2003, Spear, 2000] believed to be underlied by limitations in decision making and increased reward processing [Geier et al., 2010, Luna et al., 2010]. While cognition is reaching adult levels there are still limitations during the adolescent period in executive function believed to reflect known brain maturational processes [Luna et al., 2004, Luna et al., 2010]. One component that has been found to improve in this period is working memory.

Working memory (WM), the ability to maintain information online to guide planned voluntary behavior [Baddeley, 1992], is a core executive function supporting a wide range of behaviors. Although the rudiments of WM emerge in infancy and early childhood [Diamond et al., 1994], developmental studies indicate that WM continues to improve into adolescence [De Luca et al., 2003, Demetriou et al., 2002, Luciana et al., 2005, Luna et al., 2004, Ullman et al., 2014], with visuospatial WM in particular taking longer to develop than other types of WM, such as verbal [Demetriou et al., 2002]. For example, the ability to generate a saccadic response guided by WM is adult like by 15 years of age, whereas the precision of the WM response continues to improve late into the second decade of life [Luna et al., 2004]; notably, these findings held across different delay lengths, suggesting that maintenance processes alone do not account for behavioral improvements. Further, increasing the difficulty of

the WM task results in a larger performance gap between children and adults, such that children up to age 12 perform significantly worse on both spatial and non-spatial WM tasks when additional items must be maintained [Thomason et al., 2009], or when information must be manipulated, such as maintaining the order that the cue stimuli were presented in reverse [Crone et al., 2006]. These findings suggest that whatever the neural underpinnings of mature WM behavior, they must show protracted age-related change to support the late development of WM, and likely involve task epochs not limited to maintenance, such as encoding or retrieval.

1.2 BRAIN SYSTEMS UNDERLYING WORKING MEMORY

1.2.1 Dorsolateral Prefrontal Cortex (DLPFC)

DLPFC is known to play a primary role in WM. Studies of non-human primates performing delayed oculomotor tasks during single unit recordings in DLPFC have shown an increase in the firing rate of DLPFC neurons that is sustained during the WM delay period [Chafee and Goldman-Rakic, 1998, Compte et al., 2003, Funahashi et al., 1989], and that glutamatergic receptors in DLPFC underly this persistent firing [Wang et al., 2013]. Consistent with this, studies in humans using functional MRI (fMRI), which measures metabolic activity from the blood-oxygen level dependent (BOLD) response, have shown that DLPFC is involved in WM; a meta-analysis of 24 fMRI studies in which normative adults performed different types of WM tasks showed DLPFC activity was present across all task variations [Owen et al., 2005], and a more recent meta-analysis confirms this [Rottschy et al., 2012]. Further, fMRI studies in adults performing WM tasks have shown that delay-related DLPFC activity increases with greater memory load (ie, greater number of items or amount of information to recall) [Diwadkar et al., 2000, Linden et al., 2003, Manoach et al., 1997] and is a significant predictor of correct vs. incorrect WM trials [Pessoa et al., 2002].

In addition to these findings that DLPFC is involved in WM, there is also evidence it is necessary for WM. In monkeys performing a spatial WM task, lesions of DLPFC [Funahashi

et al., 1993] or disruption of activity via an adrenergic agonist [Mao et al., 1999] leads to WM performance decrements. In humans, DLPFC lesions and "temporary lesions" created using transcranial magnetic stimulation (TMS) degrade performance in a range of WM tasks [Bechara et al., 1998, Mottaghy et al., 2002, Oliveri et al., 2001, Owen et al., 1990, Owen et al., 1996, Zanto et al., 2011]. These findings confirm the importance of DLPFC for WM and how its function may potentially underlie WM performance improvements in development.

While the above review categorizes local and network DLPFC processes contributing to mature WM behavior, how these processes change across development, when WM is immature, is not as well understood. There is significant evidence that localized changes in DLPFC may underlie age-related improvements in WM. In post-mortem human brains, synaptogenesis and synaptic pruning show a longer developmental trajectory in DLPFC than other cortical regions. Synaptogenesis in occipital and temporal cortices peaks around 3 months, with DLPFC peaking around 15 months, and doesn't catch up to lower cortical regions until about 3.5 years of age; later in development, synaptic pruning in occipital and temporal cortex is complete by 7 and 12 years of age, respectively, while DLPFC pruning continues until mid-adolescence [Huttenlocher and Dabholkar, 1997]. Consistent with these changes, whole-brain studies of cortical thickness using magnetic resonance imaging (MRI) have shown that peak cortical thickness is reached latest in DLPFC, around 11 years of age [Shaw et al., 2008]. In addition to cortical thinning and synaptic pruning, there is a developmental increase in the activity of parvalbumin-containing inhibitory neurons that use gamma aminobutyric acid (GABA) as a neurotransmitter in the DLPFC [Lewis, 1997]. These findings suggest that delayed DLPFC development could underly protracted WM immaturities in adolescence.

In humans, there have been several developmental studies of WM using fMRI which have shown that activity in DLPFC changes with age, although findings have been mixed, with examples of greater delay period activity in children and adolescents than adults [Geier et al., 2009], greater delay activity in adults than children [Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007], as well as a U-shaped curve, with adolescents showing the greatest activity [Geier et al., 2009, Scherf et al., 2006]. Further studies have shown that these findings may depend on condition; adults show increased DLPFC activity for more

difficult trials, whereas children do not show this difference [Crone et al., 2006, Thomason et al., 2009], suggesting that they require more effort to perform at a similar level. These discrepancies also may in great part be due to cross-sectional sampling which limits the ability to assess age related change (discussed below). Due to these mixed findings, it is unclear what underlying mechanisms these age-related changes in DLPFC activity might reflect *(Aim 1)*.

1.2.2 Posterior Cortex

While DLPFC is critical and necessary for WM, it may not be sufficient, as there is a distributed circuitry known to support WM across a wide range of tasks; meta-analyses of fMRI studies of adults performing a range of WM tasks found that in addition to DLPFC, other regions were activated across tasks, including other prefrontal regions, posterior cortical regions, and subcortical regions [Owen et al., 2005, Rottschy et al., 2012]. Among these, posterior parietal cortex (PPC) has been found to be of unique significance in supporting WM. Similar to DLPFC, single cell recordings in monkeys performing WM tasks have reported elevated PPC activity during the delay period [Chafee and Goldman-Rakic, 1998, Constantinidis and Steinmetz, 1996, Qi et al., 2010]. As with the DLPFC, PPC also plays a causal role in WM; impairing PPC activity in monkeys via "selective cooling" causes WM deficits [Quintana and Fuster, 1993] as do structural and TMS PPC lesions in humans [Berryhill and Olson, 2008, Husain et al., 2001, Kessels et al., 2000, Koch et al., 2005, Malhotra et al., 2005, Oliveri et al., 2001, Pisella et al., 2004]. One aspect of the role of PPC in WM may be unique from that of the DLPFC, namely that it supports the mnemonic aspects of WM, in contrast with the DLPFC supporting the executive processes informed by WM [Postle et al., 1999]; consistent with this, studies in monkeys have found that sustained PPC activity during WM performance is more susceptible to interference than DLPFC activity [Qi et al., 2010].

Further, PPC is not the only posterior cortical region playing a role in working memory; more recent work has focused on the "Sensorimotor Hypothesis" [D'Esposito and Postle, 2015], in which visual association cortex (VAC) areas in the occipital and temporal lobes play

a key role in representing the information to be remembered in working memory, and the role of the DLPFC is executive rather than mnemonic. Recent studies have supported this, using multivariate methods to show that stimulus characteristics stored in WM are encoded in VAC [Riggall and Postle, 2012, Sneve et al., 2012, Sreenivasan et al., 2014a, Sreenivasan et al., 2014b]. Not only are posterior cortical regions involved in WM, they also show protracted development during WM, particularly in PPC and VAC [Geier et al., 2009, Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007, Scherf et al., 2006, Ullman et al., 2014]. While these studies highlight the development of activity in these regions, a key aspect of the role of posterior cortex in WM concerns its connection and interaction with DLPFC, rather than its unique local activity.

1.2.3 Connectivity

There is great interconnectivity between PFC and posterior cortical regions via the cingulum, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF) and fronto-occipital fasciculi (FOF) [Rushworth et al., 2006, Schmahmann et al., 2007]. Studies in humans using diffusion tensor imaging (DTI) have shown that some of these connections, including the SLF, ILF and cingulum, correlate with WM performance [Charlton et al., 2010, Golestani et al., 2014], underscoring the importance of fronto-posterior integration in WM.

Given that structural connections between DLPFC and PPC regions are important for WM, it is not surprising that their functional connection is important as well. In monkeys, simultaneous recordings in DLPFC and PPC demonstrated matching neural activity patterns during a WM task [Chafee and Goldman-Rakic, 1998, Quintana and Fuster, 1999]. Similarly, selective cooling of either DLPFC or PPC while recording in the other region showed that activity in these regions during WM are interdependent, such that mean firing rates in >70% of neurons recorded in DLPFC and PPC changed with disruption of the other region [Chafee and Goldman-Rakic, 2000]; both increases and decreases were evident, suggesting that complex reciprocal signaling underlies WM behavior. Consistent with these findings, a study in human adults examined functional connectivity during performance of a WM task

and found that activity in DLPFC and PPC were jointly correlated with VAC [Gazzaley et al., 2004], highlighting how fronto-posterior integration may be fundamental to WM processing. Further studies demonstrate that information travels between VAC and DLPFC regions during WM, specifically in a bottom-up fashion [Sreenivasan et al., 2014a, Sneve et al., 2015], and that fronto-posterior connectivity is correlated with performance [Gazzaley et al., 2007].

In addition to developmental trajectories in local function in DLPFC and posterior cortical regions described above, there is widespread development of neural connectivity supporting cognitive control, which may lessen dependence on PFC functions. Post-mortem study in humans show increased myelination of synaptic connections continuing into adolescence and beyond, particularly in white matter adjacent to cortical regions [Yakovlev and Lecours, 1967]. Studies in humans using MRI and DTI report that volume and microstructural integrity of tracts connecting frontal and posterior regions, including the SLF, ILF, and cingulum, show protracted development into adolescence [Asato et al., 2010, Lebel et al., 2008, Paus et al., 2001]. These studies highlight how maturation of fronto-posterior connectivity may underlie WM development.

This conclusion is reinforced by studies examining the development of functional connectivity. While no studies to date have examined the development of functional connectivity during WM, studies in other domains shed some light on how it may develop. One study examining the development of functional connectivity associated with inhibitory task performance during fMRI showed significant strengthening of prefrontal connectivity through adolescence [Hwang et al., 2010]. Further, several studies have examined the developmental of task-free/resting-state connectivity, finding protracted maturation in networks involving prefrontal and posterior cortical regions [Dosenbach et al., 2010, Fair et al., 2007]. This suggests that examining the development of connectivity supporting WM performance and how it may support WM development *(Aims 2-3)*, may be important to understanding developmental changes in BOLD activity.

Importantly though, while we have summarized the literature on the adolescent development of brain structure and function and how it supports WM, no studies have examined this in a longitudinal (3+ measurements/person) sample.

1.3 LONGITUDINAL DEVELOPMENT

1.3.1 Intra-Individual Variability

Cross-sectional studies test subjects at one time point compared to longitudinal studies, which test subjects on several occasions. The main limitation of cross-sectional studies is that they have an inherent cohort effect where individuals may be different in ways that are greater than age effects. That is, cross-sectional studies are limited in their ability to separate intra-individual and inter-individual differences, leading to greater variability and less power to detect differences.

This is where a key statistical benefit of longitudinal designs comes into play. Using *repeated measures* allows for separation of intra-individual and inter-individual components of variability [Rogosa et al., 1982, Singer and Willett, 2003]. Accounting for inter-individual differences (whatever the source) helps reveal effects that are true to actual development. Figure 1 details an example where a longitudinal study is important; despite the intra-individual developmental change being small relative to the inter-individual differences, the longitudinal data enables detection of the developmental change.

1.3.2 Individual Trajectories

The other key benefit of longitudinal data is that one can relate characteristics of growth curves, like differences in brain activation or rates of growth in brain development, to other individual differences. The most important example of this is clinical growth charts [Ogden et al., 2002], in which an individual's height, weight, and other attributes are measured when they visit the doctor, and plotted on a chart, which compares these measurements to the population trajectory. For example, two individuals whose weight roughly tracks along the curve around the 25th and 75th percentiles, respectively, are both well within the limits of normal (Figure 2a). However, an individual may also show trajectories that differ from the population curve, potentially representing more rapid growth in some individuals (Figure 2b) or halted growth/early maturation (Figure 2c). Further, data on individual trajectories also helps with identification of outliers or measurement errors (Figure 2d).

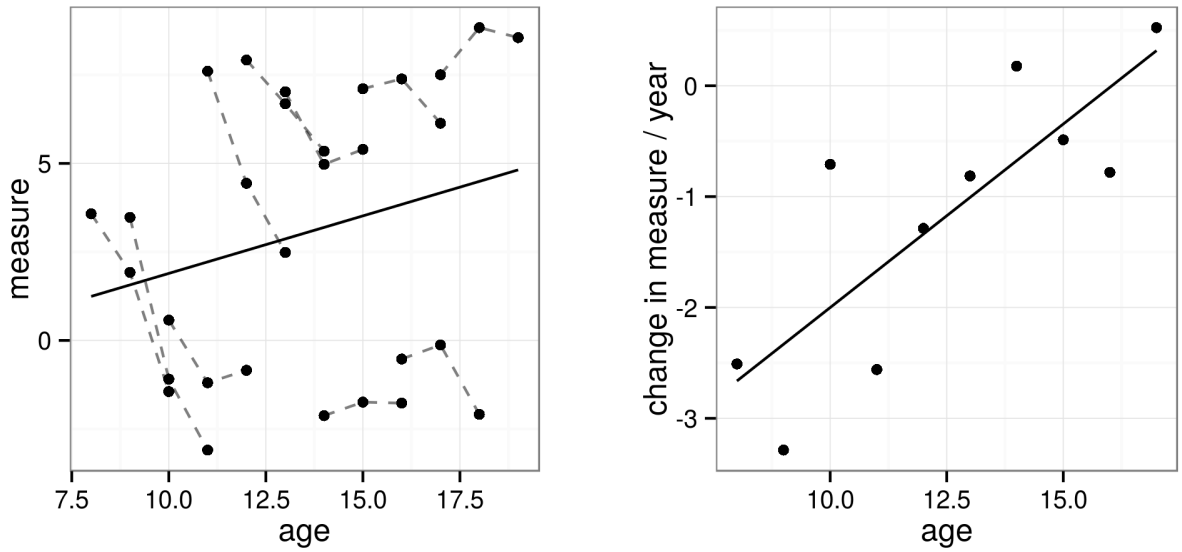
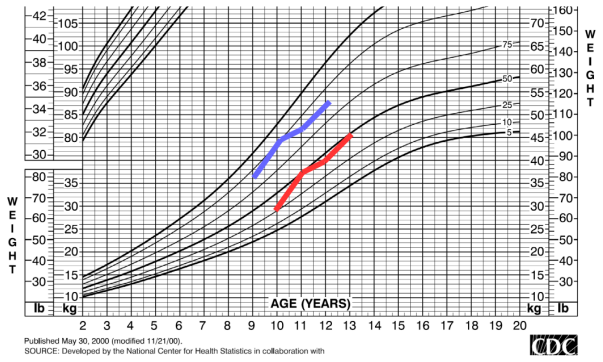
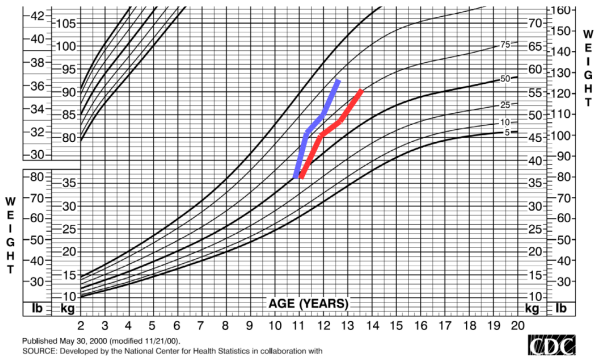


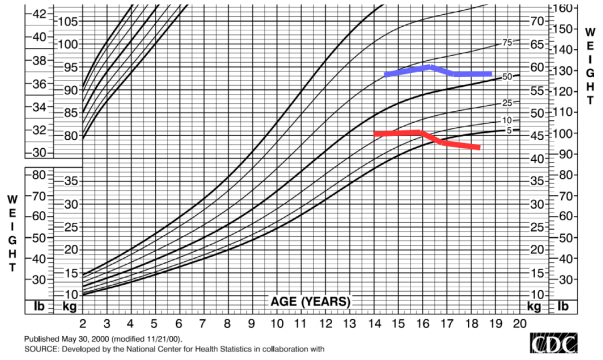
Figure 1: Example of how longitudinal data can detect developmental pattern in the presence of high inter-individual variability. Data for this example was made up to be illustrative. (Left Panel) Measurements are shown by age, with individuals connected by dashed lines. Solid line shows linear fit as if data was not longitudinal, whose fit would suggest the measure increases with age. (Right Panel) Growth rates from linear fits to each individual, plotted by their starting age. Solid line shows linear fit, demonstrating the "true" developmental effect, such that the measure decreases with age (negative growth rates), and further that this decreases are larger in early development.



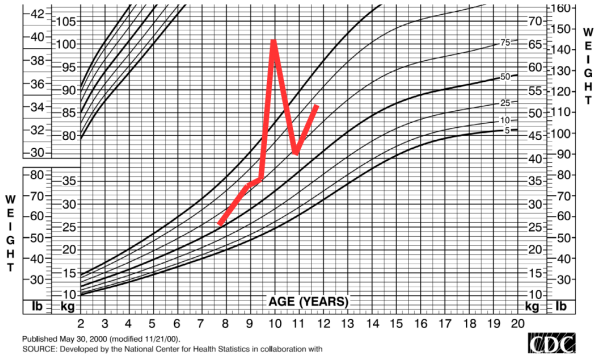
(a) Different Means



(b) Different Rates



(c) Abnormal Development



(d) Outliers

Figure 2: Examples of individual growth trajectories, plotted on normal developmental clinical growth charts for weight from the CDC. Each panel illustrates important individual differences that can be examined in longitudial data. (a) Two individuals with different means but similar rates. (b) Two individuals with similar means but different rates. (c) Similar to 'a', but crossing percentiles may be a red flag for abnormal development or pathology. (d) An individual who has been measured several times with one obviously incorrect or outlier measurement.

The most important benefit of using longitudinal data however, is that one can speak of "development" in contrast to cross-sectional studies, which can only refer to age group differences.

1.4 GOALS OF DISSERTATION

The overarching goal of this dissertation is to apply a longitudinal design to characterize age-related changes in brain activity and connectivity underlying WM development in adolescence. In this manner, we have the ability to account for inter-individual differences, there is greater power to detect developmental change, as well as the opportunity to confirm average developmental trajectories across the population within individuals. Further, by using a clinical growth chart model to characterize individual brain development, we aim to not only increase our understanding of changes occurring during adolescence but also take one step closer towards bringing developmental brain imaging into the clinic.

1.4.1 Specific Aims

The first aim of this thesis was to characterize changes in brain function underlying WM through adolescence. In this aim, we studied the trajectory of normal development in brain function using fMRI, and how they relate to WM development. Given extensive literature indicating that DLPFC is critical to WM and has a protracted developmental timecourse through adolescence, our hypothesis was that WM-related activity in DLPFC would continue to develop through adolescence and would be associated with performance.

The second aim of this thesis was to characterize changes in WM-related functional connectivity through adolescence, using fMRI. We again focused on the DLPFC and examined connectivity with other brain regions associated with WM using a beta-series analysis [Gazzaley et al., 2004, Rissman et al., 2004]. Since functional connectivity between DLPFC and posterior cortical regions has been shown to be critical for WM processing [Sreenivasan et al., 2014a, Sneve et al., 2015], and functional connectivity with prefrontal and posterior

cortical regions continues to develop through adolescence [Dosenbach et al., 2010, Fair et al., 2007, Hwang et al., 2010], we hypothesized that WM-related functional connectivity with DLPFC would increase with development, and that these increases would underlie performance improvements.

Finally, the third aim of this thesis was to characterize changes in the structure of brain connections through adolescence, using DTI. We focused on the role of the cingulum, SLF, and sagittal stratum (SS; containing the ILF/IFOF), which have been shown to mature through adolescence [Asato et al., 2010, Lebel et al., 2008, Paus et al., 2001] and are associated with WM performance [Burzynska et al., 2011, Olesen et al., 2003, Vestergaard et al., 2011], as well as peripheral white matter in the frontal, parietal, temporal and occipital lobes, which have also been shown to continue developing through adolescence [Lebel et al., 2008, Yakovlev and Lecours, 1967]. We hypothesized that protracted development of these regions would underlie improvements in WM. Further, we examined how white matter development is related to developmental changes in functional activity in DLPFC and connectivity with DLPFC, hypothesizing that development of brain function depends on the development of structural connections. Parts of this aim have already been published [Simmonds et al., 2014].

2.0 DEVELOPMENT OF FUNCTIONAL ACTIVITY ASSOCIATED WITH WM DEVELOPMENT (FMRI)

2.1 BACKGROUND

As indicated in the introduction, there have been several developmental studies of WM using fMRI, with mixed findings. Common across studies are findings that there are developmental changes in the function of DLPFC, as well as distributed brain regions, including parietal and visual association cortex [Geier et al., 2009, Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007, Scherf et al., 2006]. However, there have been several discrepancies in these studies as well, with varying directionality of DLPFC function changes with age, including greater delay activity in children and adolescents than adults [Geier et al., 2009], greater delay activity in adults than children [Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007], as well as a U-shaped curve, with adolescents showing the greatest activity [Geier et al., 2009, Scherf et al., 2006].

These discrepant findings may be due to a range of methodological differences such as choice of task and ages examined. While these studies have primarily explored visuospatial WM, they used a range of tasks within this domain, including N-back [Burzynska et al., 2011], object-memory [Crone et al., 2006], and the memory-guided saccade (MGS) task [Geier et al., 2009, Scherf et al., 2006]. Further, some of these tasks utilize extra measures that affect cognitive demands, such as a large number of items to remember or a requirement to manipulate the contents of WM, increasing the tasks difficulty. Another discrepancy may be based on contrast; adults show increased DLPFC activity for more difficult trials, whereas children do not show this difference [Crone et al., 2006, Thomason et al., 2009], suggesting that they require more effort to perform at a similar level, and that differences may be

related more to difficulty than specific WM processes. These discrepancies might contribute to differences in developmental findings between studies; hence, for the current study, we chose to use an MGS task to minimize extra cognitive demands. In addition, the MGS task used previously in a large behavioural study showed a protracted development of working memory that extended through adolescence and was consistent across different delay periods [Luna et al., 2004], suggesting that processes outside of maintenance may play an important role. Hence, we also applied an event-related design to separately examine activity associated with encoding, maintenance, and retrieval components of WM.

Further, there have been no longitudinal studies to date examining the development of WM with 3+ time points, which allows for estimation of within-individual trajectories However, there has been a recent study with a 2 time-point follow-up study [Ullman et al., 2014], which indicated that fronto-parietal activity was associated with current WM capacity, while basal ganglia regions were associated with future WM capacity. In the current aim, we build on these previous studies and utilize true longitudinal data to understand individual differences in WM development and its underlying functional correlates.

2.2 STUDY, METHODS & BEHAVIORAL DEVELOPMENT

2.2.1 Study Design

We have designed a study that incorporates the advantages noted above. The study draws from Dr. Luna's unique longitudinal study of cognitive and brain development, currently in its 9th year. 129 participants (67 female) were studied in an "accelerated longitudinal design", in which participants were enrolled at any age between 8 and 30, and returned for annual visits from that point. A total of 356 sessions with usable fMRI data (criteria detailed below) were available for analysis (mean = 2.8 visits/subj) (see Figure 3 for sample details).

Each year, participants return for two visits. In the 1st visit, they perform neuropsychology tests, eye-tracking tests and fill out various questionnaires; data from this visit is not included in this thesis. In the 2nd visit a week later, participants underwent an MRI

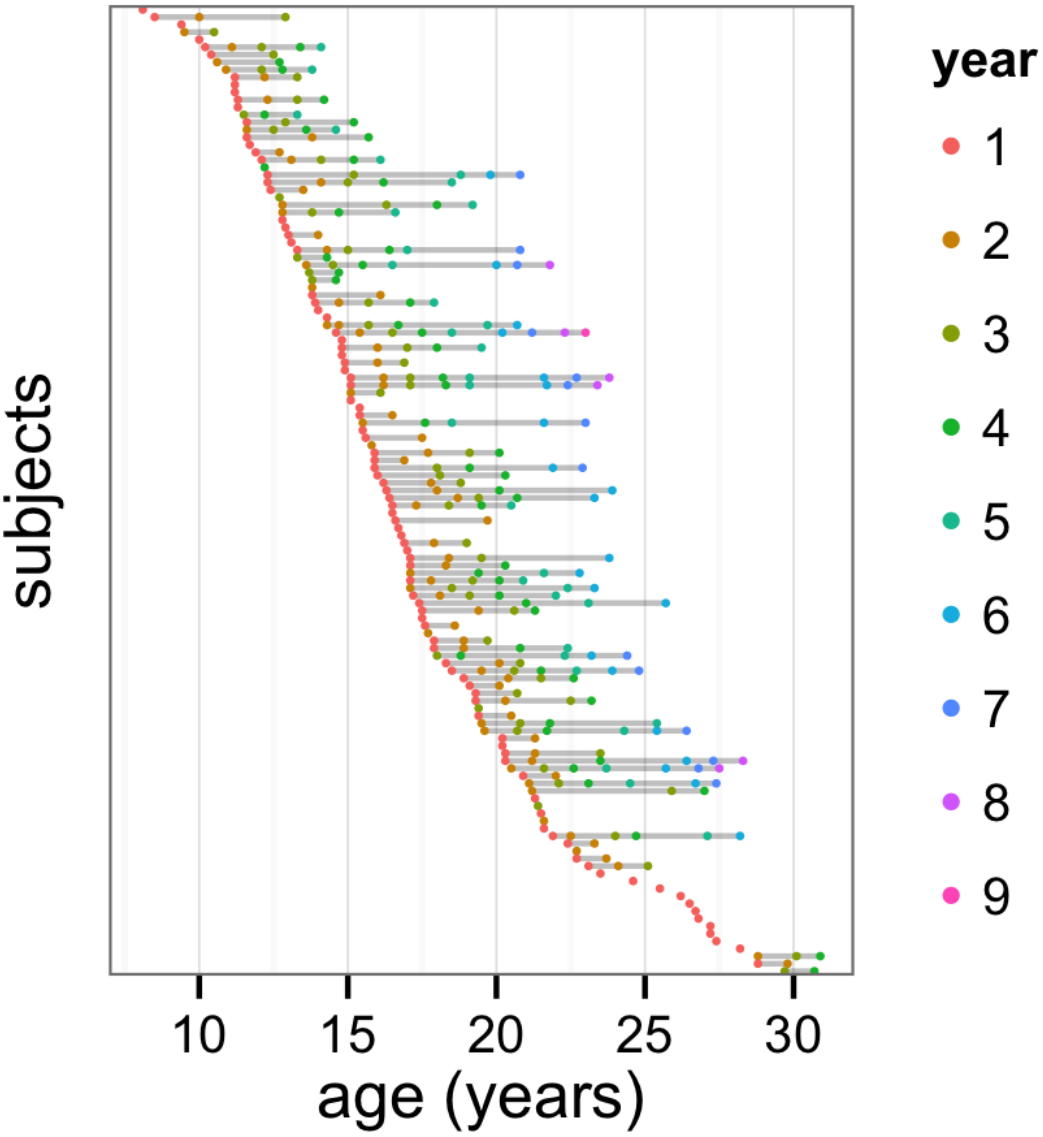


Figure 3: Distribution of ages and scans in study sample. Each point represents a time point; color represents year of study (up to 9) as indicated in the legend. Time points belonging to the same individual are connected by lines.

imaging protocol which included fMRI and DTI, the focus of the current thesis.

All participants reported no past or current neurological or psychiatric disorders, no family history of these disorders in first-degree relatives and no contra-indications for scanning (such as claustrophobia or metal implants). All participants had intelligence quotient (IQ) tested using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981) and none had a full scale IQ of less than 80 (IQ at first visit: 107 $\pm$ 10). All participants gave informed consent and were compensated for their time. All experiments complied with the Code of Ethics of the World Medical Association (1996 Declaration of Helsinki) and were approved by the Institutional Review Board at the University of Pittsburgh.

2.2.2 Task

For this study, participants performed a memory-guided saccade (MGS) task [Hikosaka and Wurtz, 1983], otherwise known as the oculomotor delayed response (ODR) task [Funahashi et al., 1989]. In this task, a participant maintains fixation and is presented with a peripheral **cue** stimulus in an unexpected location, which the participant *encodes* into WM. After the stimulus disappears, the participant returns their gaze to fixation and *maintains* it during the **delay** period until the **target** signal (fixation disappears), at which time the participant *retrieves* the information to guide an executive saccade to the remembered location. We used a variant of this task in which participants made a saccade to the cue stimulus, rather than maintaining fixation, before maintaining fixation during the delay period (see Figure 4 for task illustration). This variant was critical to avoid potential inhibitory demands in children and to gain information regarding encoding processes of WM.

We selected the MGS task for two main reasons. First, we chose to study visuospatial WM instead of verbal or other types due to its protracted developmental timecourse [Demetriou et al., 2002]. Second, the task has minimal extra cognitive demands. It is less confounded by verbal strategies, the stimulus and response are in the same domain [Luna et al., 2004]. There are also no high load or manipulation conditions, so the results are less likely to be confounded by task difficulty, and more likely to be successfully performed by children and adolescents. Importantly, performance is measured as the accuracy of the sac-

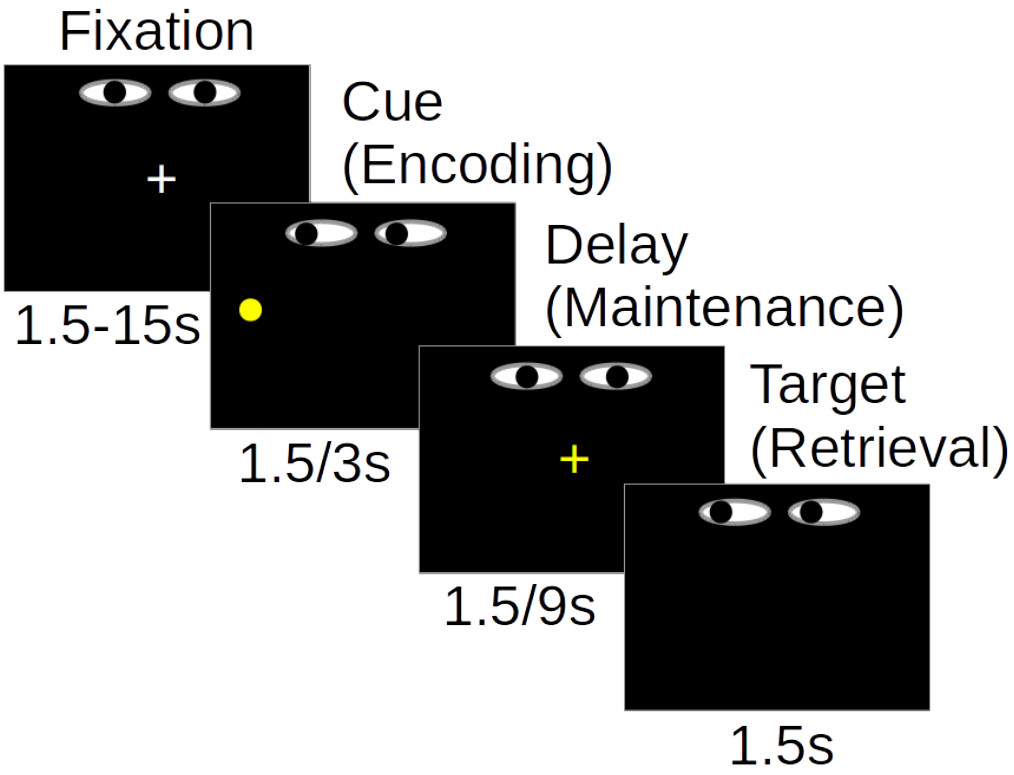


Figure 4: Illustration of a trial in the MGS task. The label for each epoch is shown above its image, the duration below the image. Cartoon of eyes at top of each epoch image indicate where participant's gaze should be. Initially, a participant maintains fixation for 1.5-15s before being presented with a peripheral **cue** stimulus in an unexpected location, which the participant *encodes* into WM. After the stimulus disappears, the participant returns their gaze to fixation and *maintains* it during the **delay** period until the **target** signal (fixation disappears), at which time the participant *retrieves* the information to guide an executive saccade to the remembered location.

cade to the remembered location providing a continuous measurement of behaviour, which if more sensitive to development than typical yes/no WM tasks. Finally, the MGS task has been employed extensively in nonhuman primate studies, which has allowed for its underlying neural circuitry to be determined at the cellular level [Barbas, 2000, Funahashi et al., 1989, Funahashi et al., 1993, Hikosaka and Wurtz, 1983].

Participants performed 3 runs of the MGS task, each containing 20 trials, evenly split into short (1.5s)/long (3s) encode periods, and short (1.5s)/long (9s) delay periods, followed by a 1.5s retrieval period. Fixation between trials was jittered between 1.5-15s.

2.2.2.1 Analysis Eye-movement data were analyzed and scored using in-house scripts in R [R Core Team, 2012]. Saccades were identified using a velocity algorithm using a 20 s criterion, and blink-related artifacts were identified and corresponding trials discarded. Each eye movement trial was scored for performance accuracy (correct, incorrect, or dropped due to blinks or instrument error). A run within a session was excluded if there were less than 10 correct trials out of 20; further, a session was excluded if it contained less than 20 correct trials across runs.

Primary measures of interest were *latency*, measured as the time from the end of the delay (fixation disappears) to the onset of the memory-guided saccade, and *precision*, measured as the difference in degrees between the initial saccade and the target position, relative to the initial encoding saccade.

2.2.3 Developmental Analyses

2.2.3.1 Mixed Models In order to integrate our longitudinal design, we used *linear mixed-effects regression* [Pinheiro and Bates, 2000]. In mixed models, *fixed effects* represent the average growth trajectory in the sample while *random effects* account for individual variability around mean growth parameters [Singer and Willett, 2003]. Mixed models are especially powerful because they do not require binning and have no problems with missing data. Mixed models were used in all longitudinal analyses in the study, as implemented in R using the lme4 package [Pinheiro and Bates, 2000]. For each analysis, outliers were

identified by removing each time point from the model, refitting and predicting the missing time point, then calculating prediction error; those exceeding 2.5 standard deviations from the mean were excluded. Further, in analyses where multiple ROIs are examined, a Holm correction for multiple comparisons was used [Holm, 1979]; this is similar to a Bonferroni correction but less stringent, since the threshold becomes more lenient with each significant region.

2.2.3.2 Developmental Timing While it is evident that there are significant changes in behavior and brain processing during adolescence, the timing of these changes is poorly understood. There are two approaches to studying adolescent development that have been most commonly applied in human imaging studies.

In a cross-sectional group approach, studies often use an adolescent group (typically 13-17) in comparison to a child group (typically 8-12) and/or an adult group (typically 18 and up) (e.g. [Geier et al., 2009, Scherf et al., 2006]). This design is powerful in that you need fewer subjects to find a significant effect. However, as indicated earlier, adolescence may extend into both the child and adult group definitions, obscuring the group differences that would represent "adolescent development". One method that has occasionally been used to address this limitation is "Change Point Detection", in which smaller age bins are used (eg 1 year), and adjacent age bins are statistically compared; when the difference is no longer significant, maturity has been reached (e.g. [Luna et al., 2004]). By comparison, this method requires significantly more subjects, due to the larger number of groups and can only be used in a cross-sectional design.

More commonly, studies have used regression with age as a continuous variable. This method allows for full age coverage with fewer subjects than would be needed for a change-point analysis. The trade-off is that one must select a model (or range of models) to fit the data. The most common age models used to represent adolescent development are linear, inverse, and quadratic.

Linear indicates the age-related change is occurring (either increasing or decreasing), with no signs of slowing. While this is often sufficient for studies examining small age ranges, this is not appropriate for a study investigating changes into adulthood when development

should reach stability [Burchinal and Appelbaum, 1991, Kail, 1993, Luna et al., 2004].

Inverse indicates that age-related change is occurring (either increasing or decreasing), but its magnitude changes with development, representing large changes earlier in development, and smaller changes later. While the inverse model has been reported to be the best fit model in cognitive development [Luna et al., 2004, Ordaz et al., 2013], it can miss changes in processes that peak during adolescence.

Quadratic indicates that age-related change is occurring, but that a peak is reached during adolescence, after which there is age-related change in the opposite direction. Developmental changes in several important systems, such as dopamine, show this pattern [Spear, 2000], and several studies have shown that some prefrontal activity during WM shows this pattern as well [Geier et al., 2009, Scherf et al., 2006].

While the quadratic model can provide a peak time, none of these models provide any information about maturation time. Some studies have tried to address this issue using arbitrary cut-offs; for example, one study defined maturation time as the time the model predicted 90% of the maximum value [Lebel et al., 2008]. We have developed a technique that uses smooth, piece-wise regression to capture information about the shape and timing of development, including time of maturation. The technique is also capable of localizing unique "stages" of development when the most rapid changes are occurring.

2.2.3.3 Finding Developmental Stages Figure 5 illustrates the steps of this technique. The first step of the technique involves finding a model that makes less assumptions about the shape of the developmental trajectory than the linear, inverse, and quadratic models. One model that meets this need is a *spline* model, in which piecewise polynomials are fit, specified at pre-selected ages, or *knots*. More specifically, a "natural spline" model is useful in that it reduces the number of terms required for these fits (one per cubic polynomial), allowing more power to detect effects. Initially, a series of models at different knots are generated with the most parsimonious model selected based on Bayesian Information Criterion (BIC). If the selected model is significant (determined using a log-likelihood test against an intercept-only model), we then move on to the next step of the technique.

In the second step, an intercept-only model is fit to the data to estimate the variance, and

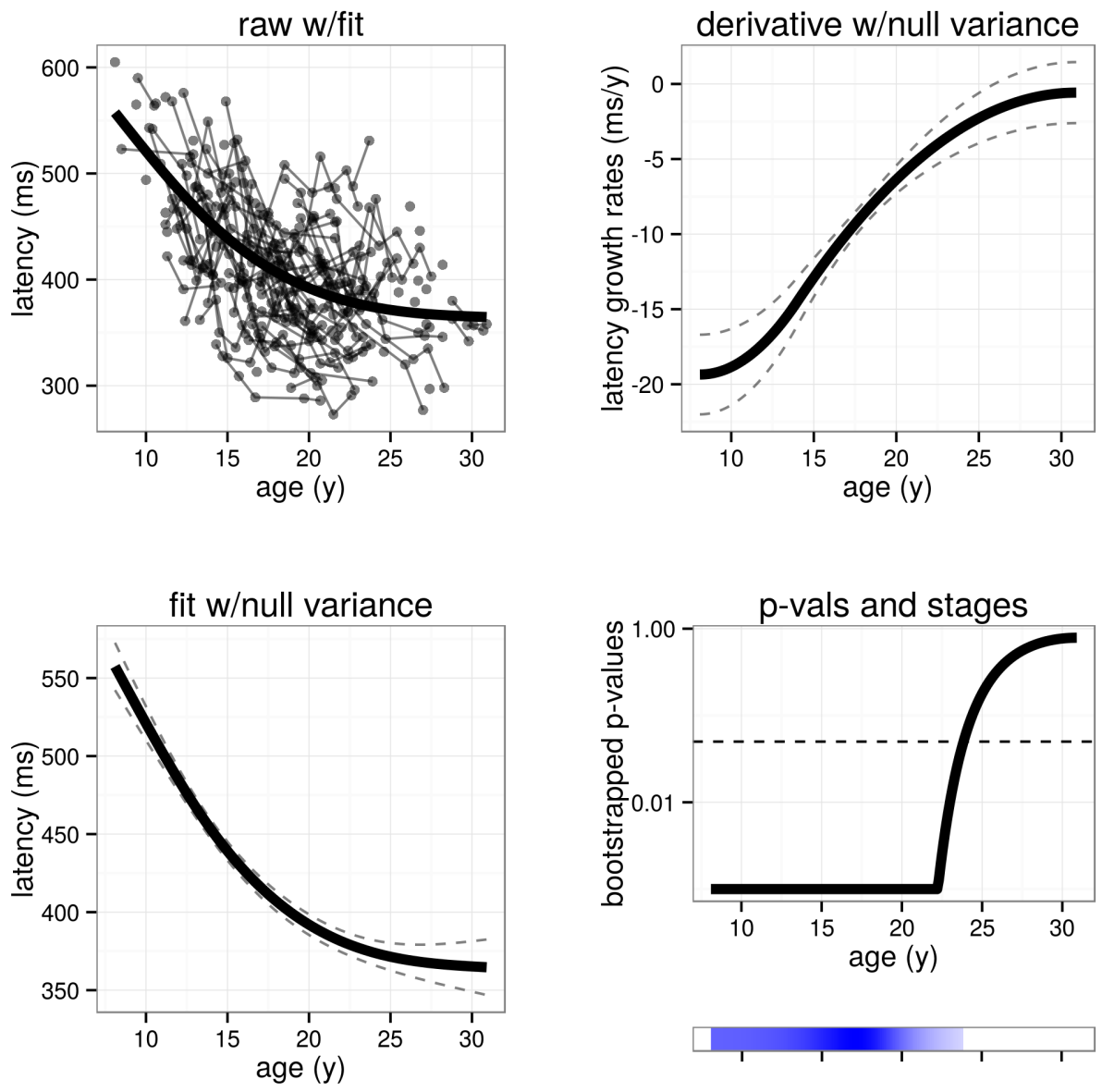


Figure 5: Illustration of method used to detect stages from data, using latency as an example. (Top Left) Raw latency values plotted by age, with measurements in the same individual connected by lines. (Bottom Left) Spline model fit showing decreases in latency with age. Dashed lines indicate 1 standard deviation from fit line derived from bootstrapping. (Top Right) Derivative of model fit showing decreases in latency with age. Dashed lines again indicate 1 standard deviation from fit line derived from bootstrapping. (Bottom Right) P-values derived from bootstrapping, with colored portion of bar underneath indicating stages of growth (red = increasing, blue = decreasing). Dashed line indicates p = 0.05.

new null data (stripped of age effects) is simulated a large number of times (1000). The spline model is fit to each set of null data, and from this a null age distribution is generated. For both the actual data and null distribution, data is predicted at small age intervals (1/10th years). At each age point, a p-value is drawn from a Z distribution based on (predicted actual data - mean of null distribution) / (std. dev. of null distribution). However, we are typically not interested in the difference from the mean, but rather in whether age-related change is occurring or not, which leads to one more step.

In the third step, an instantaneous derivative, representing the velocity or *growth rate* at each interval of the predicted data from the fit model is calculated; the same is done for the fits to the null data. As with step 2, a p-value is drawn from a Z distribution, but in this case, it represents whether growth at that point is *significantly different from zero*. The point at which growth is no longer significantly different from zero ($p>0.05$) is a *non-arbitrary* definition for maturity. This analysis is capable of revealing linear, inverse, and quadratic patterns discussed above. Further, it is not limited to these patterns, but is also capable of detecting complex patterns and multiple stages of growth. This technique is our primary analysis method in this study.

We chose to focus on rate of change rather than mean levels previously examined in order to quantify growth. The rationale for this approach is similar to population growth charts, where a particular individual could be in the 25th percentile and be mature, or in the 75th percentile but still growing. Previous studies have inferred maturational status by rationally chosen, but arbitrary, mean-level based thresholds, such as 90% of the maximum [Lebel et al., 2008] or the mean of all subjects 18 years and older [Dosenbach et al., 2010]. Both of these metrics are strongly influenced by the age range included in the study. However, by using growth rates, a less arbitrary threshold can be set: the point at which growth is no longer significantly different from zero represents maturity. Further, this approach allows the potential identification of multiple distinct stages of growth, with intermediate periods of slow/no growth. A similar methodological approach has been utilized to study nonlinear growth patterns using electroencephalography (EEG) [Thatcher, 1992], but remains unexplored in adolescence.

2.2.3.4 Stages of Interaction We applied the same principle described in the previous section to study brain-behavior and functional-structural relationships in this study (see Figures 6 and 7 for example). The primary model contained an interaction of age (spline) and the interacting variable. Rather than simulating from an intercept-only model, however, we simulated from a model that contained age and the interacting variable, but no interaction term. In this case, the result from the 2nd step above is now meaningful; it represents stages of development when *mean levels* of the dependent variable are related to the interacting variables.

The 3rd step above is meaningful as well. It represents stages of development when *rates of change* in the dependent variable are related to the interacting variables. This case is especially interesting, because it implies directionality (for example, being an above average performer on the task predicting brain growth for the following year).

2.2.4 Behavioral Results

There were robust developmental changes in both measures of WM performance (latency: p<1e-15; precision: p=2.5e-07) (see Figure 8). In both cases, decreases in latency and precision error were seen at the start of the sample in childhood (8.1) and continuing early into the third decade (maturation time: latency=23.8, precision=20).

2.3 FUNCTIONAL BRAIN DEVELOPMENT

2.3.1 fMRI Acquisition and Preprocessing

A 3T MR Siemens MAGNETOM Allegra scanner (Erlangen, Germany) with a standard circularity-polarized head coil was used to acquire imaging data. Before the study scan participants were trained to remain still in a "mock" scan that provided auditory feedback about head motion. In addition, pillows were used to stabilize the head inside the head coil during study scans, and earplugs were used to reduce scanner noise. Visual stimuli were presented using EPrime (Psychology Software Tools, Pittsburgh, PA) software on a

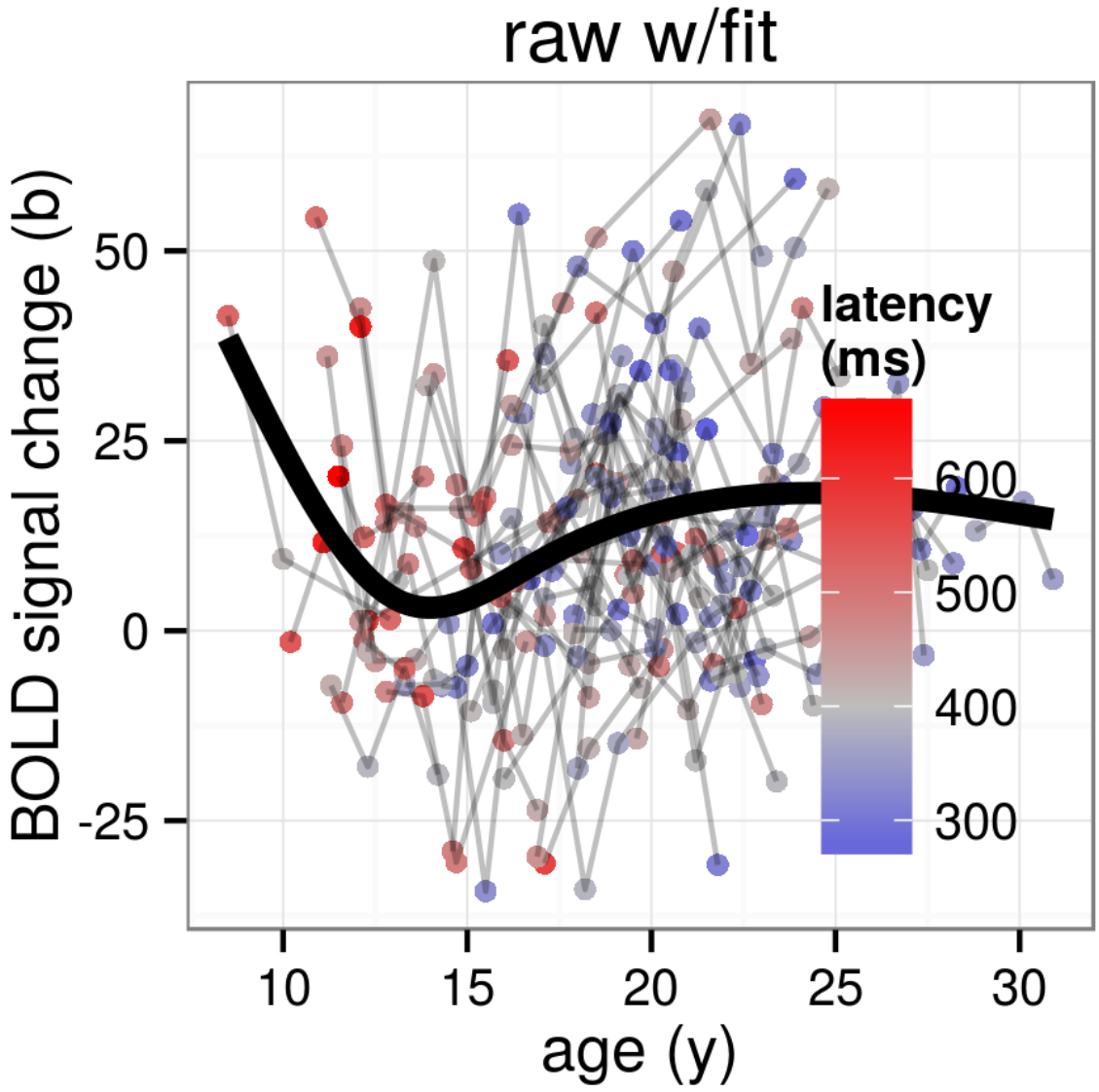


Figure 6: Example of a 3-way interaction with age, brain and behavior, using BOLD activity (plotted on the Y-axis) and latency (blue = faster, red = slower). Measurements within the same individual are connected by lines. Method to detect stages of interaction in this example is illustrated in Figure 7.

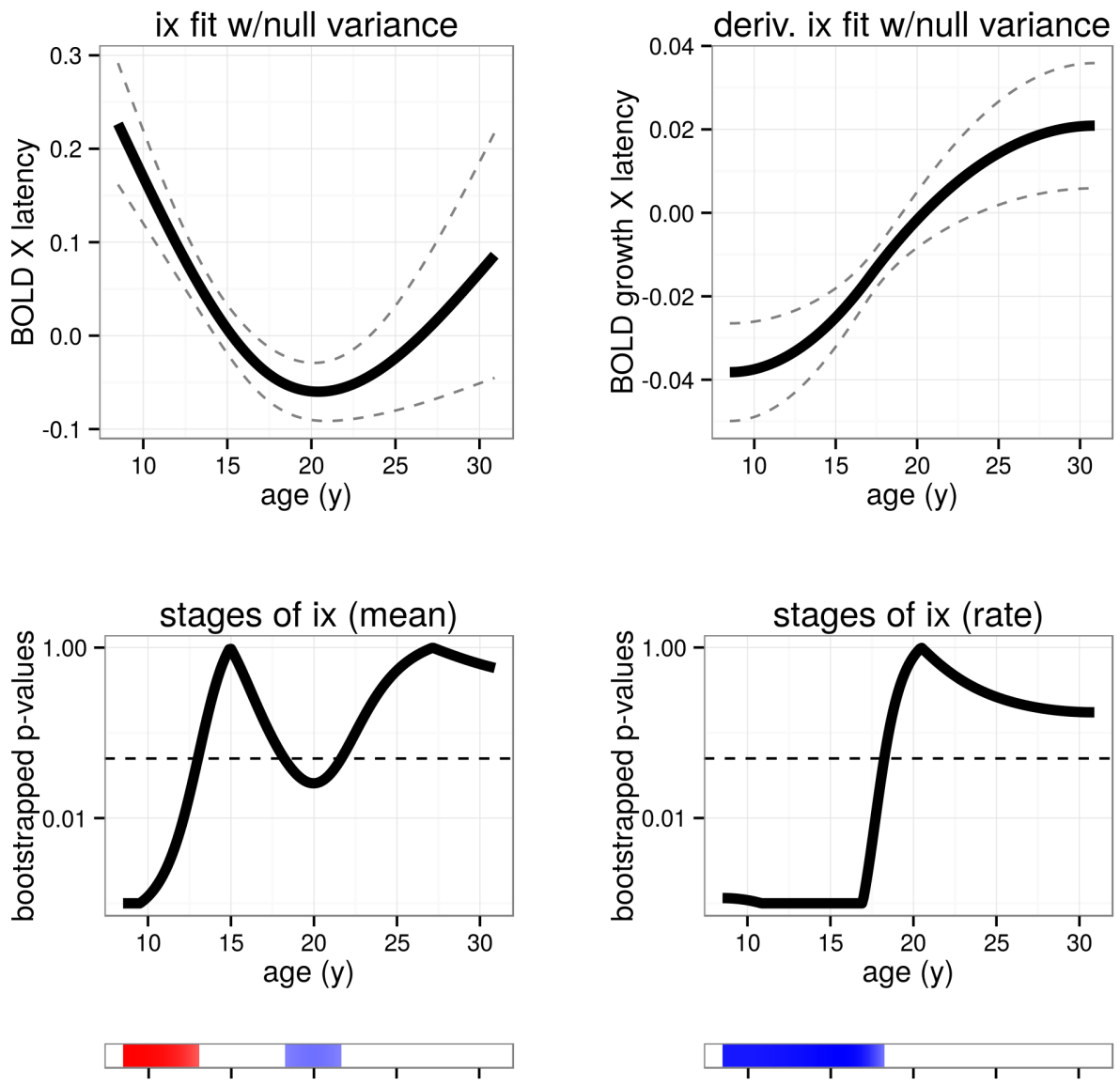


Figure 7: Illustration of method used to detect stages of interaction, using BOLD activity and latency as an example; raw data is illustrated in Figure 6. (Top Left) Spline model fit showing changes in the slope between brain and behavior with age. Dashed lines indicate 1 standard deviation from interaction fit line derived from bootstrapping. (Bottom Left) P-values derived from bootstrapping, with colored portion of bar underneath indicating stages of interaction with mean levels of BOLD activity (red = positive, blue = negative). Dashed line indicates p = 0.05. (Top Right) Derivative of model fit showing changes in the slope between brain growth and behavior with age. Dashed lines again indicate 1 standard deviation from fit line derived from bootstrapping. (Bottom Right) P-values derived from bootstrapping, with colored portion of bar underneath indicating stages of interaction with rates of growth in BOLD activity (red = positive, blue = negative). Dashed line indicates p = 0.05.

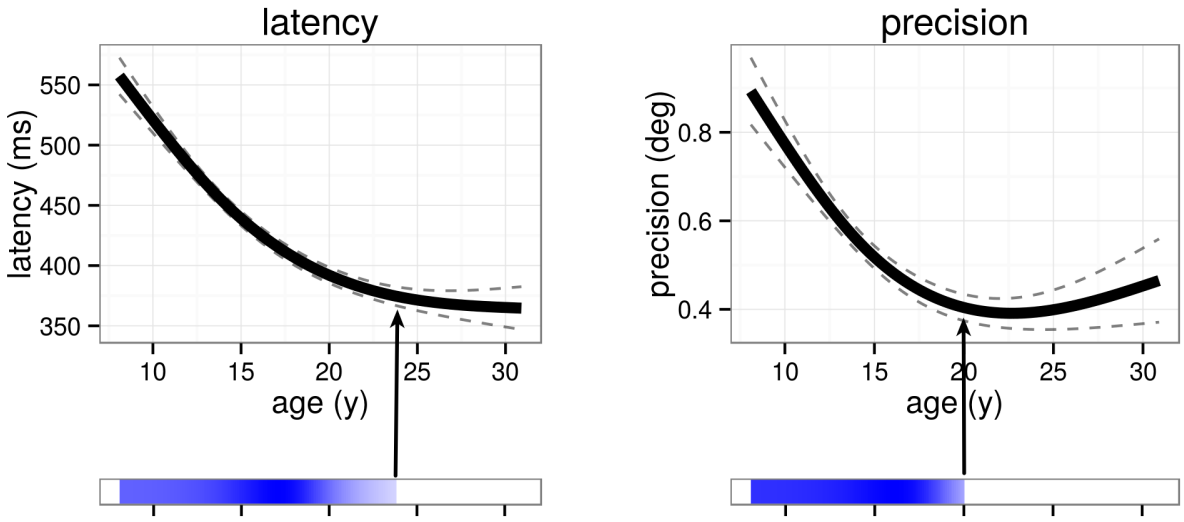


Figure 8: Behavioral results showing that both latency (left) and precision (right) decrease into early adulthood. Solid line indicates spline model fit and dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (red = increasing, blue = decreasing).

dedicated computer (Dell Dimension 8200, Pentium 4, 2 GHz, Windows XP). Stimuli were projected onto a translucent rear projection screen attached to the scanner bore above the chest, which participants viewed through via a mirror attached to the head coil.

A high-resolution structural image was acquired using a sagittal magnetization-prepared rapid gradient-echo T1-weighted sequence (MPRAGE; repetition time=1570 ms; echo time=3.04 ms; flip angle=8; inversion time=800 ms, voxel size = 0.78125 x 0.78125 x 1 mm), which was used for the alignment of functional images. Functional images were acquired using a type of echoplanar imaging that is sensitive to BOLD contrast [T2*], with standard parameters (repetition time=1500 ms; echo time=25 ms; flip angle=70; voxel size=3.125 x 3.125 mm in-plane resolution, 29 4mm slices, AC-PC aligned). Participants performed four functional runs of an antisaccade task (25 minutes total) prior to performance of three runs of the MGS task (each run contains 229 volumes, length=5'43"). The first six images in each run were discarded to allow stabilization of longitudinal magnetization.

fMRI data were preprocessed using a standard pipeline using FSL (FMRIB, Oxford, UK) and AFNI (NIH, Bethesda, MD) software. fMRI data were initially converted from raw DICOM images to NIFTI format, followed by application of slice time correction, rigid-body motion correction, normalization to template (Montreal Neurological Institute; MNI) while resampling to 3mm isotropic voxels, and temporal/spatial smoothing. Voxelwise data were normalized to 10000 X global median, an alternative to voxel-wise normalization for calculating percent signal change. Structural and functional data were manually inspected to ensure data integrity, including artifacts due to motion.

2.3.2 fMRI Analysis

Individual fMRI data were analyzed using a general linear model (GLM) in AFNI. Correct, error, and dropped trials were modeled using a gamma function, with separate regressors for each task epoch (cue, delay, target), and baseline signal drift entered as covariates. Volumes with motion were addressed by censoring a volume and its preceding volume, if the derivative value of the volume's motion had a Euclidean norm above 1mm, to minimize potential confounds [Power et al., 2012, Siegel et al., 2014]; motion parameter estimates

were not included as covariates, as this approach has been shown to be ineffective relative to censoring alone [Siegel et al., 2014]. Contrasts for each epoch were generated by including only correct trials and were contrasted implicitly with the fixation baseline.

For fMRI group analysis, we divided the sample into two groups (see Figure 9). A cross-sectional sample (n=72, 34 female) was used for voxelwise analyses to identify regions of interest to use in the longitudinal analyses and avoid circularity. A longitudinal sample (n=57, 33 female, 259 sessions, 4.5 scans/subject) was used to characterize developmental change in more detail, using the methodology described above and regions defined in the cross-sectional sample.

2.3.3 Regions involved in WM (cross-sectional)

A one-sample t-test was performed on individual contrast maps for each task epoch. Whole-brain maps were thresholded at p=0.001 and with a minimum cluster size of 9 voxels, corresponding to a corrected p=0.05 level, as determined by AFNI's Alphasim program. Maps from each epoch were combined through a conjunction analysis, using a slightly stricter threshold for multiple comparisons ($0.001/3 = 0.0033$), and again clustered at 9 voxels.

Results revealed the canonical widely distributed circuitry engaged in WM (see Figure 10 and Table 1). Sensorimotor-related WM processes (encoding, retrieval) most robustly engaged posterior cortical regions, whereas maintenance was more associated with prefrontal regions.

2.3.4 Development of DLPFC Activity and Relation to WM Performance

Activity in the R DLPFC cluster found in the cross-sectional conjunction was then examined in the longitudinal sample; no significant developmental change was seen (p=0.43). After controlling for age (inverse), an association was seen between DLPFC maintenance activity and WM performance, specifically latency (p=0.021), such that lower activity was associated with faster responding (more adult-like performance; see Figure 11).

We next investigated whether other regions in the WM circuitry derived from the conjunction analysis contributed to the protracted development of WM performance. Due to

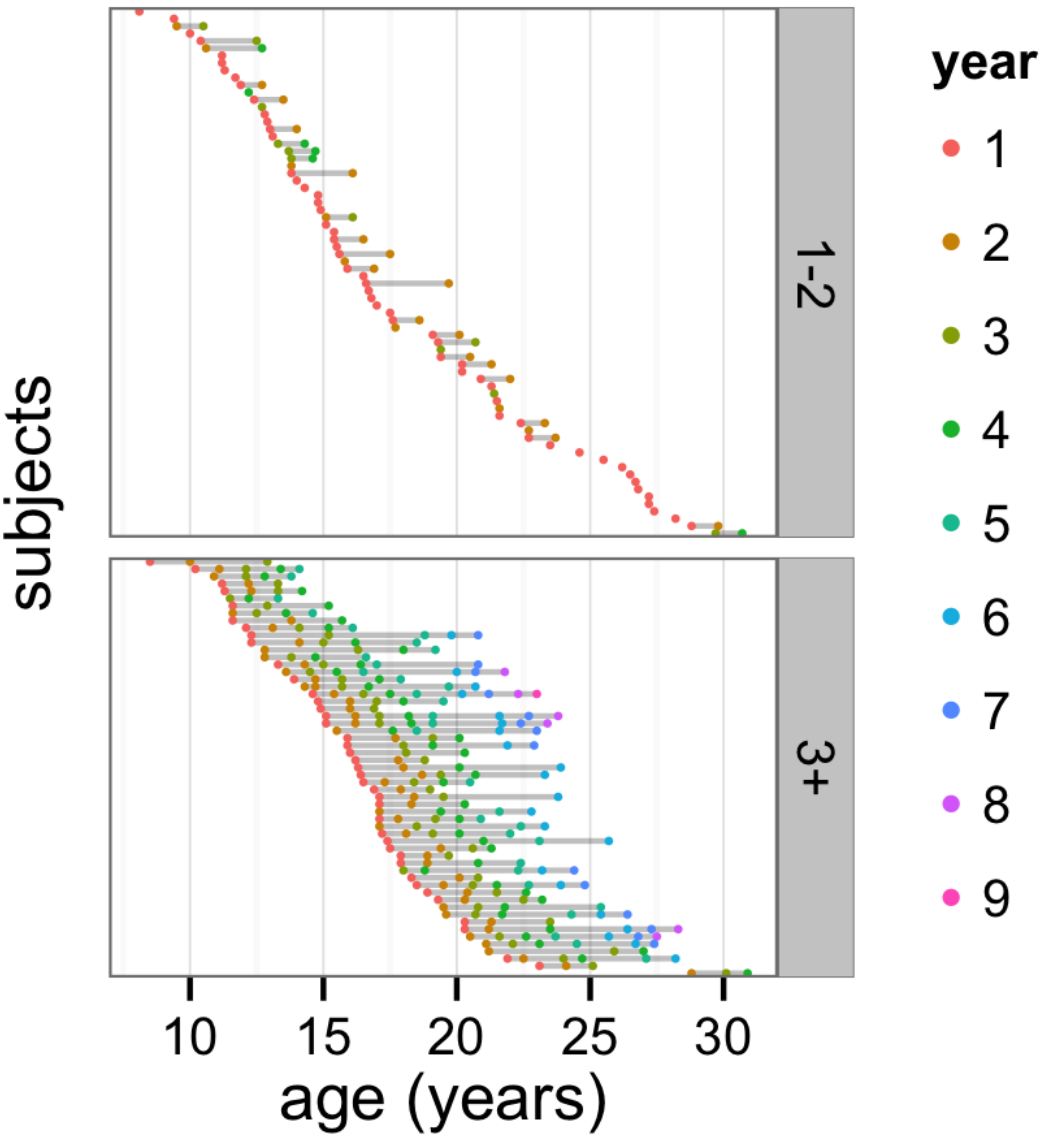


Figure 9: Distribution of ages and scans in study sample, with individuals separated into cross-sectional and longitudinal samples. Each point represents a time point; color represents year of study (up to 9) as indicated in the legend. Time points belonging to the same individual are connected by lines.

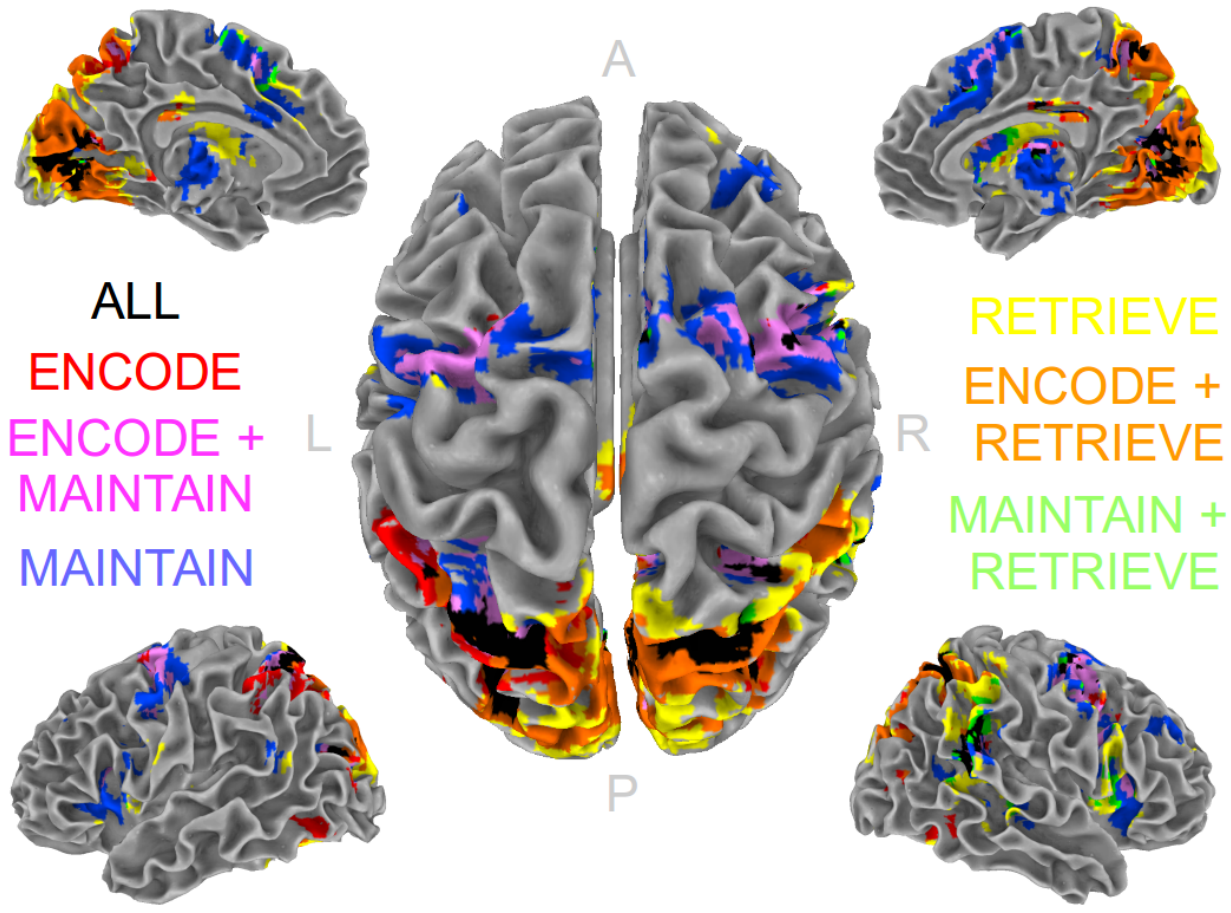


Figure 10: Surface maps detailing regions active during WM across ages in cross-sectional sample, as derived from the conjunction analysis, revealing the canonical widely distributed circuitry engaged in WM. Colors indicate that a voxel was active in an epoch-specific pattern (red = encoding, blue = maintenance, yellow = retrieval). Further, blends of these colors indicate a voxel was active during multiple epochs (purple = encoding/maintanance, orange = encoding/retrieval, green = maintenance/retrieval); black indicates activity across all 3 epochs. Right hemisphere is on the right of the image, and vice versa. For the axial view, anterior is on top; for the sagittal views, medial is on top.

Volume	X	Y	Z	Hemi	BA	Description
223452	4	-67	19	B	17/18/19/20/39	Occipital
				B	5/7/40	Inf/Sup Parietal
				B	5/7	Precuneus
				R	40	Supramarginal
				R	22/42	Mid/Sup Temporal
				B		Cerebellum
114480	7	6	25	B	6/8	FEF
				B	6/8	SMA
				B	24/32	Ant Cingulate
				R	44/47	VLPFC
				B		Ant Insula
				B		Caudate
				B		Putamen
				B		Pallidum
				B		Thalamus
3321	34	44	29	R	46	DLPFC
2457	0	-26	30	B	23	Mid Cingulate
2025	-31	-19	4	L		Putamen
1377	-55	-49	18	L	21/22	Mid Temporal
972	52	-46	-10	R	20/37	Inf Temporal
567	39	-77	7	R	19	Mid Occipital
378	1	-30	-33	B		Subcortical
351	27	59	25	R	46	DLPFC
351	-35	35	33	L	9/46	DLPFC
324	0	-40	7	B	29	Post Cingulate
297	-64	-1	19	L	43	Postcentral

Table 1: Clusters from conjunction analysis showing regions engaged in WM across ages in the cross-sectional sample. Coordinates are in MNI space, with negative numbers referring to left, posterior, and inferior, respectively. Volume is indicated in mm^3 (1 voxel = 27 mm^3). Abbreviations: Hemi=Hemisphere, B=Bilateral, R=Right, L=Left, BA=Brodmann Area, Inf=Inferior, Mid=Middle, Sup=Superior, Ant=Anterior, Post=Posterior, FEF=Frontal Eye Fields, SMA= Supplementary Motor Area, DLPFC=Dorsolateral Prefrontal Cortex, VLPFC= Ventrolateral Prefrontal Cortex.

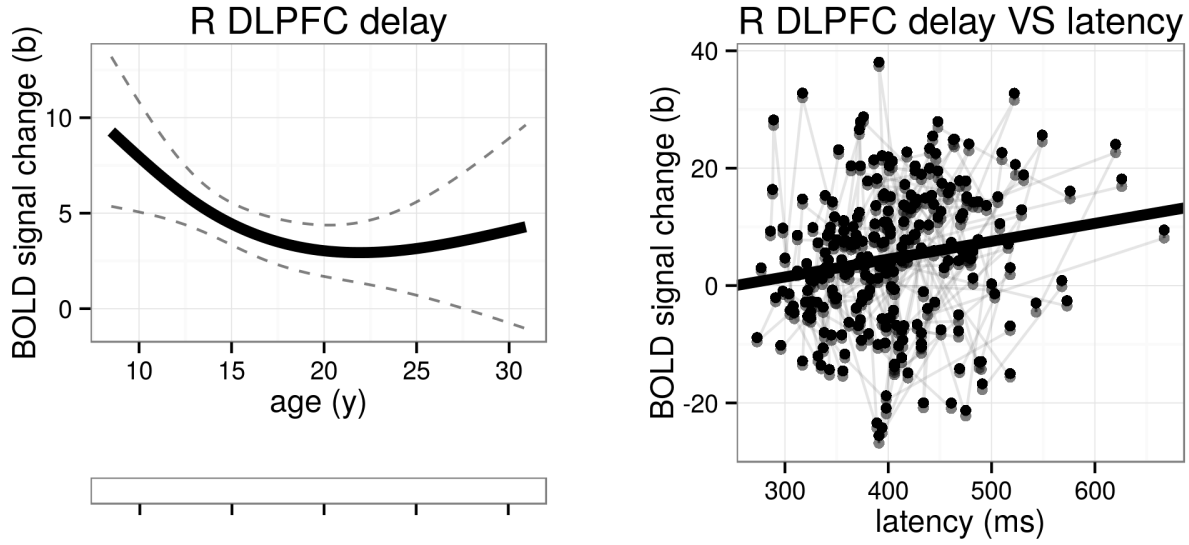


Figure 11: Association of age (left) and WM latency (right) with DLPFC maintenance activity. (Left) Solid line indicates spline model fit and dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (empty, no developmental change). (Right) Raw data is shown in gray; points in the same individual are connected by lines. Black points and line indicating corrected data after controlling for an inverse effect of age. Solid line indicates a positive correlation between activity and latency, such that greater DLPFC activity is associated with slower responding.

the extensive activation seen in the conjunction, we sought to look for more focal refinements in WM-related brain function by deriving regions showing significant age effects in the cross-sectional sample.

2.3.5 Regions showing change with development (cross-sectional)

A voxelwise regression was performed on individual contrast maps for each task epoch, correlated with age. Three different age models were examined (linear, inverse, quadratic); within each epoch, any voxel showing a significant effect for any model at p=0.001/3 was then entered into a conjunction analysis combining the epochs, with a minimum cluster size of 9 voxels. A subset of regions in the core WM circuitry showed developmental change in the cross-sectional sample; age related changes during encoding and maintenance were predominantly in prefrontal and parietal regions, while changes during encoding and retrieval were seen in VAC regions (see Figure 12 and Table 2 for details). These ROIs were then examined in the longitudinal sample.

2.3.6 Development of Other Cortical Activity and Relation to WM Performance

During encoding, linear increases reflecting decreases in activity suppression were seen with development in bilateral postcentral gyrus (PoG) during encoding (R: p=9.2e-05, stages=8.5-24.6; L: p=0.0016, stages=17-27.9) (see Figure 13).

Maintenance activity in R FEF showed a U-shaped developmental trajectory (p=1.3e-04; stages=8.5-13.3, 14.7-20.7), such that activity decreased during childhood, and increased from mid-adolescence to early adulthood. Further, development of maintenance activity in R FEF was associated with WM performance (p=0.0011; stages=8.2-18.2), such that higher rates of growth in activity were associated with faster responding (see Fgure 14).

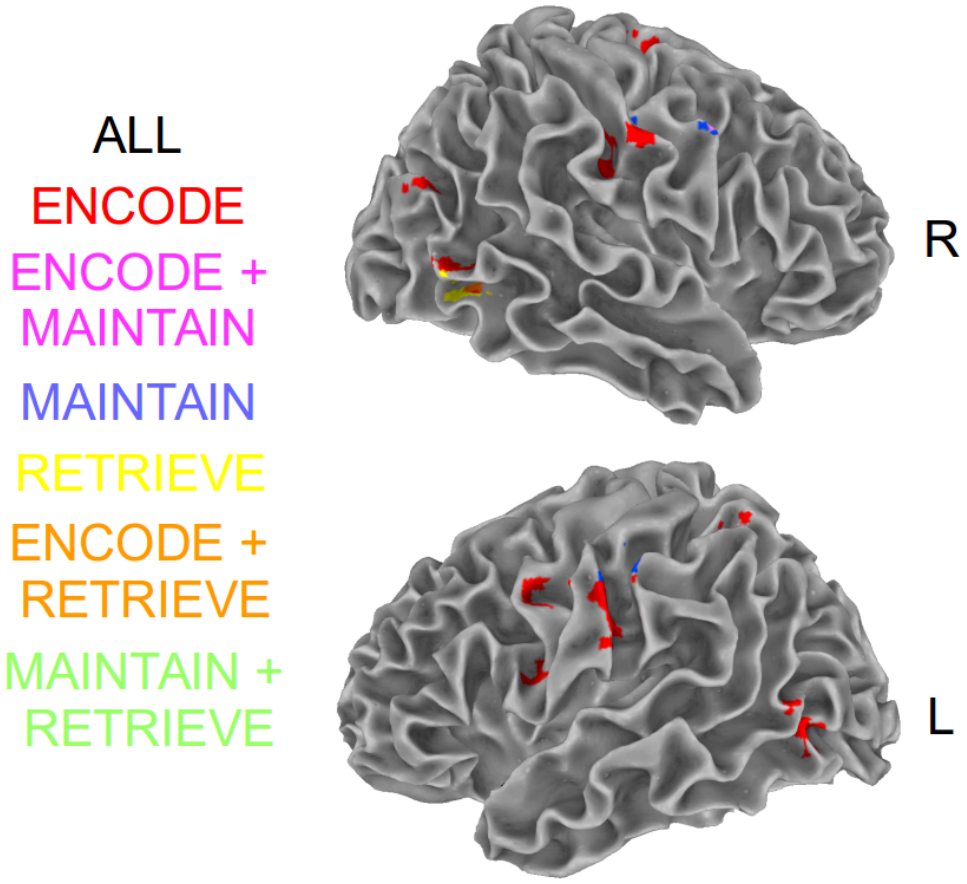


Figure 12: Surface maps detailing regions whose activity changes with age in cross-sectional sample, as derived from the conjunction analysis, revealing the canonical widely distributed circuitry engaged in WM. Colors indicate that developmental changes in a voxel's activity were epoch-specific pattern (red = encoding, blue = maintenance, yellow = retrieval). Further, blends of these colors indicate a voxel was active during multiple epochs (purple = encoding/maintanance, orange = encoding/retrieval, green = maintenance/retrieval). All regions identified were epoch-specific; no regions showed activity changing across all 3 epochs.

Volume	X	Y	Z	Hemi	BA	Description
1674	-60	-19	34	L	3/43	Postcentral
1242	51	-62	-4	R	37	Mid/Sup Temporal
756	-50	-70	-1	L	19/37	Inf/Mid Occipital
						Mid Temporal
540	-59	1	36	L	6/4	Pre/Postcentral
486	49	-23	29	R	3	Postcentral
432	-49	0	14	L	6/44	Inf Frontal
432	58	-15	37	R	3/43	Postcentral
405	-40	-56	60	L	7/40	Inf/Sup Parietal
351	54	7	40	R	6	FEF
351	21	-11	67	R	6	SEF
324	45	-22	-24	R	20/37	Fusiform/Inf Temporal
324	44	-76	23	R	39	Mid Occipital
297	23	-53	-9	R	19/37	Fusiform

Table 2: Clusters from conjunction analysis whose activity changes with age in cross-sectional sample, highlighting a small subset of cortical regions engaged in WM processing. Coordinates are in MNI space, with negative numbers referring to left, posterior, and inferior, respectively. Volume is indicated in mm^3 (1 voxel = 27 mm^3). Abbreviations: Hemi=Hemisphere, R=Right, L=Left, BA=Brodmann Area, Inf=Inferior, Mid=Middle, Sup=Superior, FEF=Frontal Eye Fields, SEF=Supplementary Eye Fields.

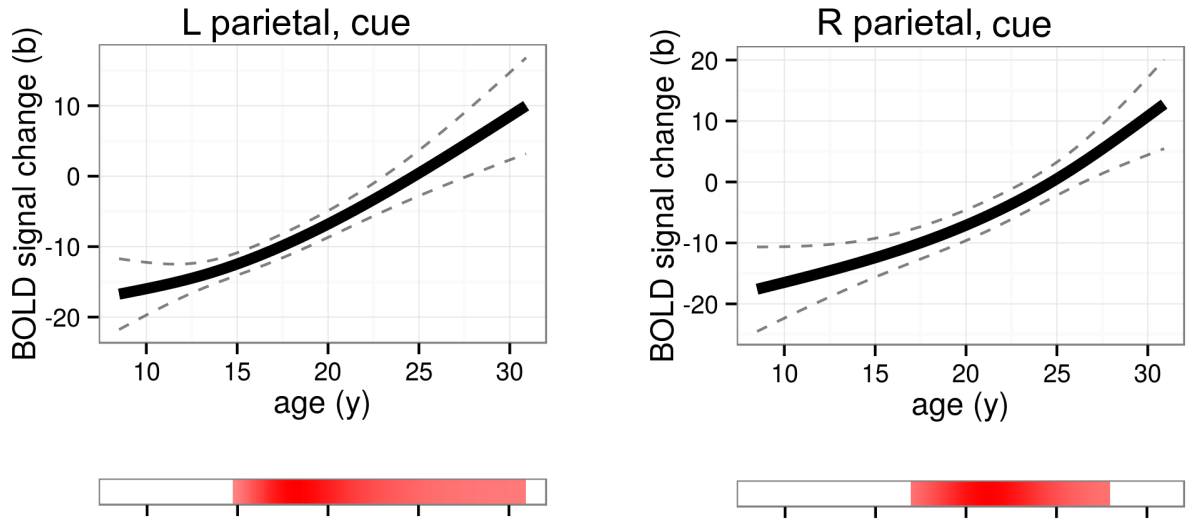


Figure 13: Solid line indicates spline model fit showing developmental increases in left and right postcentral gyrus (PoG) encoding activity into adulthood. Dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (red = increasing, blue = decreasing).

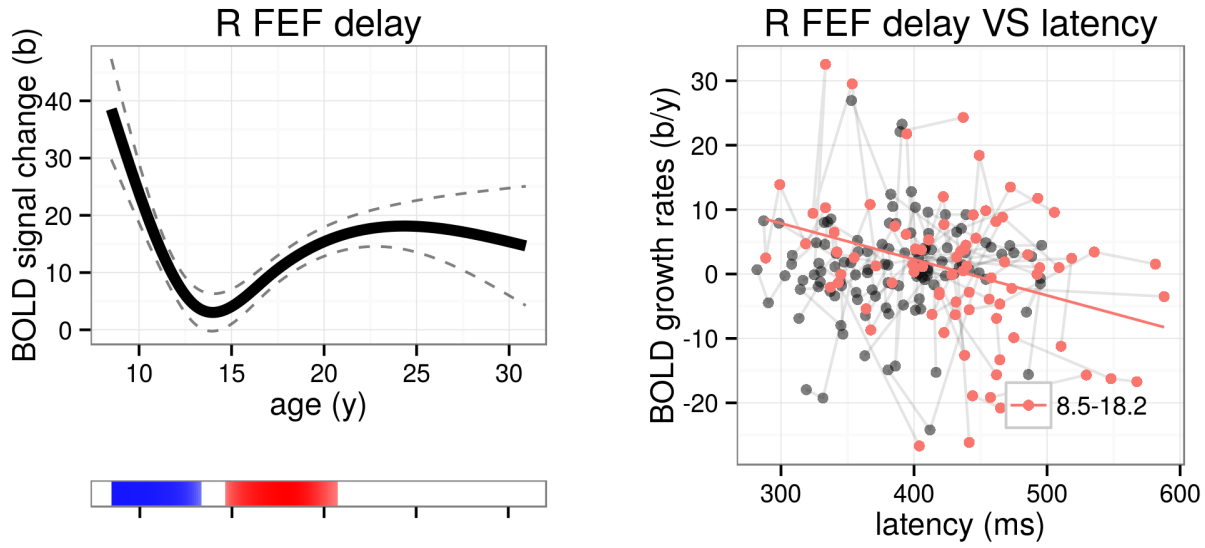


Figure 14: Association of age (left) and interaction with WM latency (right) with FEF maintenance activity. (Left) Solid line indicates spline model fit showing a U-shaped developmental trajectory in right FEF maintenance activity. Dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (red = increasing, blue = decreasing). (Right) Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored. The colored line indicates a negative correlation between development of FEF activity and latency, such that greater developmental increases in activity in childhood and adolescence were associated with faster responding.

2.4 DISCUSSION

Consistent with previous studies, we found that a widespread group of cortical and subcortical regions were engaged in various steps of WM processing [Owen et al., 2005, Rottschy et al., 2012], with most of this circuitry being engaged equivalently across ages. Notably, while DLPFC was robustly engaged in WM, specifically during maintenance, its activity did not change with development, consistent with evidence that DLPFC is recruited similarly in adolescents and adults in cognitive control [Ordaz et al., 2013]. Instead, developmental changes were seen in other regions, specifically FEF and PoG.

Developmental decreases in suppression of PoG were seen during encoding. PoG is known to be important for attention [Corbetta, 1998, Corbetta and Shulman, 2002], suggesting a greater role for attention processes in WM with development. However, since these developmental changes were not associated with WM performance, it more likely that executive processes drive WM development.

FEF is known to play in the executive control of eye movements and WM [Munoz and Everling, 2004, Postle et al., 2000, Schall et al., 2002], and is recruited to a greater degree when WM is necessary to guide responding [Barber et al., 2013]. FEF activity during maintenance was highest in childhood, and reached its lowest levels in adolescence before increasing into adulthood; further, rapid growth in this activity during this time was associated with more mature WM performance. These findings suggest that refinement of executive processes in the FEF support adolescent WM development, although it bears noting that the brain-behavior finding only accounted for development through adolescence (up to 18.2) and not later developmental improvements into the 20's. Given that we found developmental changes in regions connected with DLPFC but not in levels of activity in DLPFC itself, we next asked whether changes in DLPFC *connectivity*, rather than activity, might contribute to late developmental improvements in WM.

3.0 DEVELOPMENT OF FUNCTIONAL CONNECTIVITY ASSOCIATED WITH WM DEVELOPMENT (FMRI)

3.1 BACKGROUND

As detailed in the previous aim, activation in specific prefrontal and parietal regions in the WM circuitry (FEF, PoG) showed developmental changes through adolescence that are associated with WM performance. There are several anatomical connections between these regions and DLPFC, as well as other regions of the WM network; hence, it stands to reason that developmental change in BOLD signal in these regions may be related to their connectivity. While no studies to date have examined the development of functional connectivity during WM performance, studies have shown that functional connectivity between DLPFC and posterior cortical regions underlies WM processing [Sreenivasan et al., 2014a, Sneve et al., 2015]. If adult behavior is associated with this connectivity, it suggests the connectivity may change over development as well. While task-based functional connectivity hasnt been examined in the development of WM, task-free or resting-state connectivity has been found to go through important changes through adolescence [Dosenbach et al., 2010, Fair et al., 2007]. Further, although not involving WM, task-based functional connectivity with prefrontal cortex during inhibitory control has shown protracted development through adolescence [Hwang et al., 2010].

3.2 METHODS

FMRI data acquisition/preprocessing is the same as that used in Aim 1.

To examine functional connectivity during task performance, we used a *beta-series* approach [Gazzaley et al., 2004, Rissman et al., 2004], in which individual regressors are fit to each trial, and a correlation of the beta-series between regions indicates the degree of functional connectivity. This method can also be described as a "noise correlation" [Shadlen and Newsome, 1994]. As, with Aim 1, we only examined correct trials. Individual regressors for each correct trial and epoch were entered into a GLM model and convolved with the hemodynamic response.

The beta-series for each participant was extracted from the DLPFC ROI in Aim 1, for use as a connectivity seed region. After censoring outlier betas (>2.5 standard deviations from mean), voxel-wise correlations with DLPFC were calculated separately for each task epoch, controlling for cue and delay length.

3.3 RESULTS

3.3.1 Regions associated with development of DLPFC connectivity during WM (cross-sectional)

We examined connectivity between the DLPFC and the set of ROIs from Aim 1 that were associated with development in the cross-sectional sample. As with Aim 1, we derived an additional set of regions based on a whole-brain regression analysis with age; in this case the regions represent developmental changes in connectivity with DLPFC instead of developmental changes in activity, and a conjunction analysis was used to merge data across epochs. Whole-brain results showed that connectivity decreased between DLPFC several medial prefrontal and cingulate regions (including anterior, middle and posterior) (see Figure 15 and Table 3).

Both sets of ROIs were examined in the longitudinal sample.

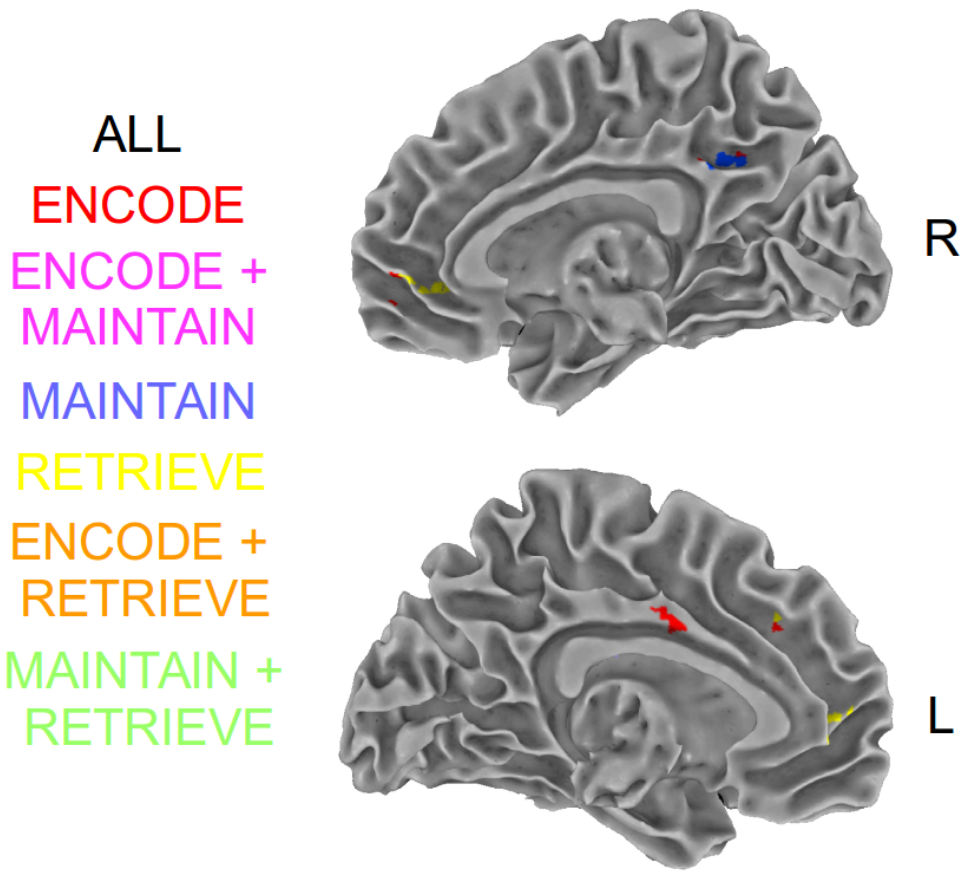


Figure 15: Surface maps detailing regions whose connectivity with DLPFC changes with age in cross-sectional sample, as derived from the conjunction analysis, revealing regions in the medial prefrontal and cingulate cortex. Colors indicate that developmental changes in a voxel's connectivity to DLPFC were epoch-specific pattern (red = encoding, blue = maintenance, yellow = retrieval). Further, blends of these colors indicate that developmental change in a voxel's connectivity to DLPFC occurred during multiple epochs (purple = encoding/maintanance, orange = encoding/retrieval, green = maintenance/retrieval). All regions identified were epoch-specific; no regions showed connectivity changing across all 3 epochs.

Volume	X	Y	Z	Hemi	BA	Description
378	3	51	-3	B	11	Med Prefrontal
324	-6	-3	35	L	23/24	Mid Cingulate
297	9	42	-3	R	11	Ant Cingulate
297	10	-50	35	R	23	Mid/Post Cingulate
270	-8	32	35	L	32	Ant Cingulate
243	-8	50	5	L	10	Med Prefrontal

Table 3: Clusters from conjunction analysis whose connectivity with DLPFC changes with age in cross-sectional sample, highlighting a small medial subset of cortical regions engaged in WM processing. Coordinates are in MNI space, with negative numbers referring to left, posterior, and inferior, respectively. Volume is indicated in mm^3 (1 voxel = 27 mm^3). Abbreviations: Hemi=Hemisphere, B=Bilateral, R=Right, L=Left, BA=Brodmann Area, Ant=Anterior, Mid=Middle, Post=Posterior, Med=Medial.

3.3.2 Development of DLPFC Connectivity and Relation to WM Performance (longitudinal)

Across all epochs, age-related increases in DLPFC connectivity with VAC (all $p<0.0031$) and decreases with middle cingulate (all $p<0.0073$) were present (see Figure 16). In both cases, connectivity continued to change into the third decade of life (maturation times = 22.4-30.9), and was higher for retrieval than for encoding or maintenance.

Further, development of DLPFC connectivity with VAC and cingulate in the retrieval epoch was associated with WM performance during late adolescence and early adulthood (see Figure 17). Specificially, this association was seen with VAC ($p = 0.0011$; stages = 16.5-30.9yo), such that higher rates of growth were associated with slow responding, and anterior cingulate ($p = 0.0069$; stages = 15.9-23.7yo), whereby more rapid decreases in connectivity were associated with faster responding.

There was also developmental change between DLPFC and FEF, specific to encoding (p=2.7e-04; see Figure 18). Mirroring the U-shaped developmental pattern of activity seen in FEF during maintenance, connectivity between DLPFC and FEF showed an inverted U trajectory, such that connectivity increased during childhood (8.5-12.9yo) and decreased in late adolescence/early adulthood (15.8-22.9yo).

3.4 DISCUSSION

This study is the first to examine the development of functional connectivity during WM performance. As with the BOLD activation in DLPFC associated with WM, many DLPFC connections do not show developmental change, suggesting that DLPFC connectivity is mostly adult-like early in development. A key subgroup of DLPFC connections however showed robust changes with development. DLPFC connectivity to mid-cingulate and FEF decreased with age while DLPFC connectivity to VAC increased. This pattern has also been seen in developmental studies of resting state connectivity, in which decreases in connectivity with DLPFC were seen in the cingulate and other prefrontal regions, while increases were

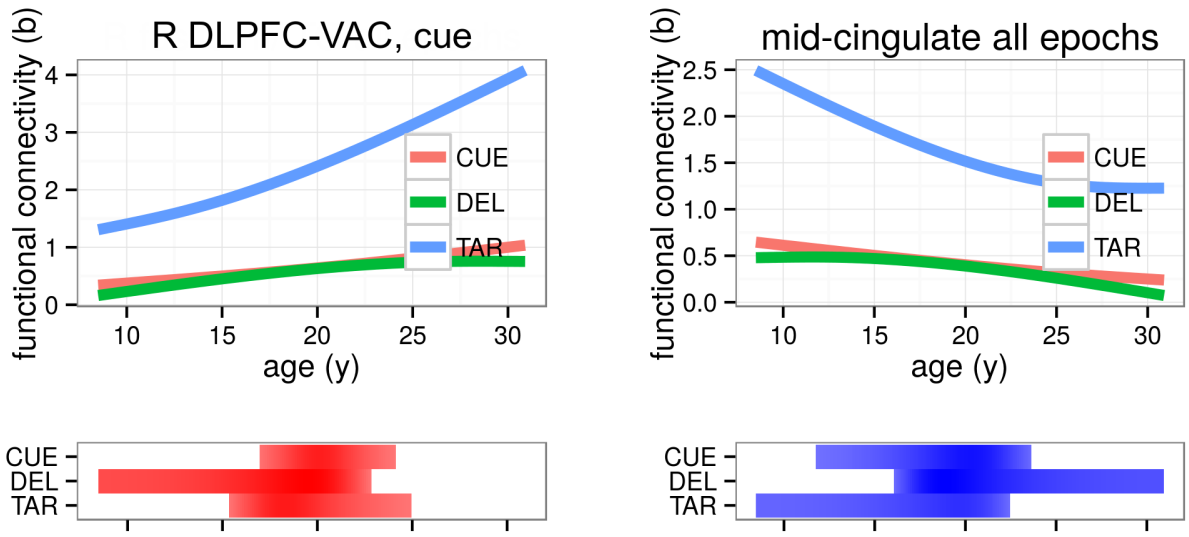


Figure 16: Developmental changes in DLPFC connectivity were seen across all task epochs into early adulthood, representing decreases in mid-cingulate (left) and increases in VAC (right). Solid lines indicate spline model fits, and the heat plot beneath highlights developmental stages (red = increasing, blue = decreasing).

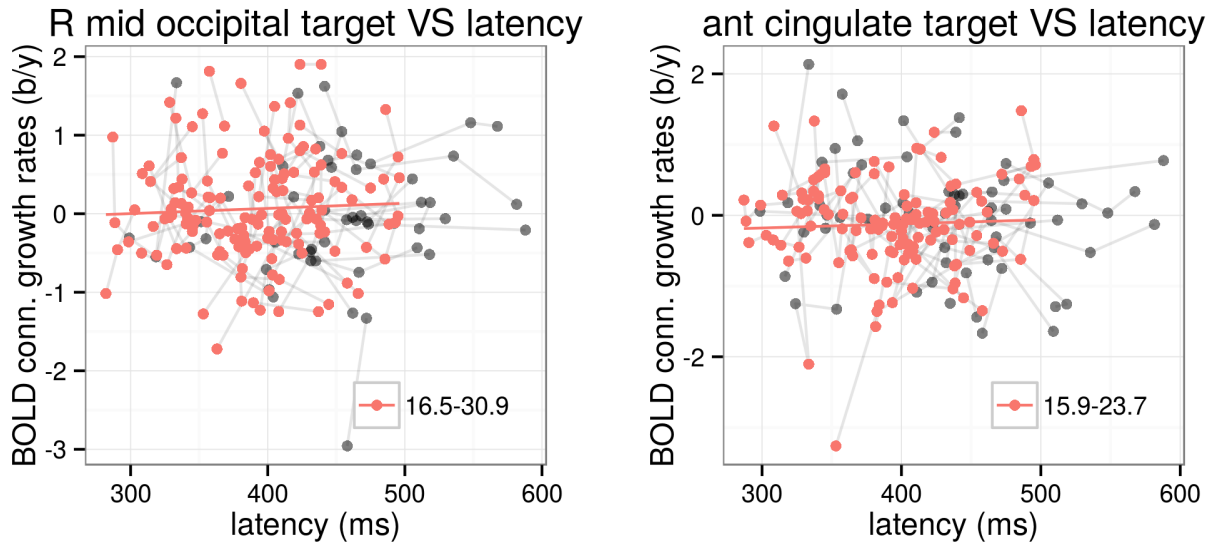


Figure 17: Developmental changes in DLPFC connectivity during retrieval with VAC (left) and anterior cingulate (right) were associated with WM performance in late adolescence/adulthood, in both cases showing that faster connectivity growth in late development is associated with slower responding. Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored, as labeled in the legend within each plot. The colored line indicates a positive correlation between development of DLPFC connectivity and latency, such that greater developmental increases in connectivity in late development were associated with slower responding.

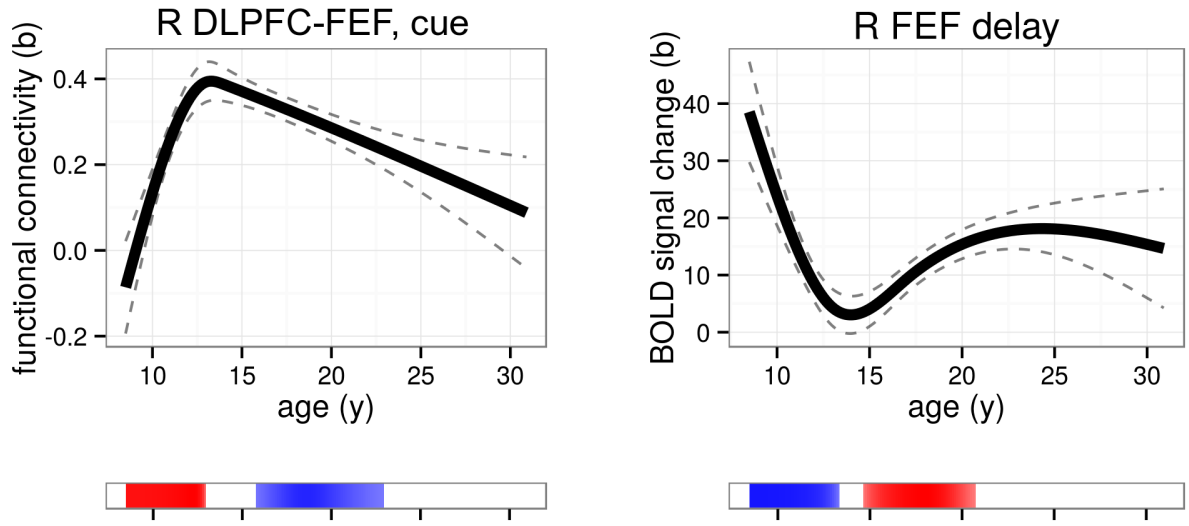


Figure 18: Developmental changes in DLPFC-FEF connectivity during encoding (left) mirror developmental changes in FEF maintenance activity (right). (Left) Solid line indicates spline model fit showing an inverted U-shaped developmental trajectory in right DLPFC-FEF connectivity during encoding, peaking in adolescence. Dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (red = increasing, blue = decreasing). (Left) Solid line indicates spline model fit showing a U-shaped developmental trajectory in right FEF maintenance activity, reaching its lowest levels in adolescence. Dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping. Heat plot beneath highlights developmental stages (red = increasing, blue = decreasing).

seen with PPC and cerebellar regions [Fair et al., 2007]. Further, although this was the first developmental study of task-based functional connectivity during WM using fMRI, these findings are consistent with those seen during inhibitory task performance where prefrontal-posterior connectivity strengthened through adolescence in parallel with improved inhibitory control performance [Hwang et al., 2010].

While much of the focus on the neural correlates of WM focus on DLPFC, newer studies have shown that VAC, including regions of occipital and temporal cortex, support the mnemonic processes underlying WM performance, whereas the role of the DLPFC is executive in planning and directing of the response [D'Esposito and Postle, 2015]. Elevated activity levels in VAC have been reported during WM maintenance [Sneve et al., 2012], and multivariate methods show that stimulus characteristics stored in WM are encoded in visual association regions and not in DLPFC, which does not encode stimulus characteristics [Riggall and Postle, 2012, Sneve et al., 2012, Sreenivasan et al., 2014a, Sreenivasan et al., 2014b]. Importantly, studies in human adults show that DLPFC/VAC connectivity underlies WM [Sneve et al., 2015, Sreenivasan et al., 2014a], and this connectivity is correlated with memory performance [Gazzaley et al., 2007]; further, resting state studies show increases in connectivity between DLPFC and posterior cortical regions [Dosenbach et al., 2010, Fair et al., 2007]. Taken together with our findings of protracted development of DLPFC/VAC connectivity and its association with WM performance in late adolescence and early adulthood, this suggests that maturation of communication between prefrontal executive regions and posterior regions specialized for processing and storing information underlies mature WM performance.

The cingulate cortex is also known to be important for WM, as it has a gradient of functional regions from ventral prefrontal cortex to parietal regions supporting cognitive, motor, and socio-emotional processing [Kelly et al., 2009]. The cingulate is widely connected throughout the brain with the middle portion connected extensively to prefrontal and posterior cortical regions [Kelly et al., 2009] and greater segregation of cingulate networks is associated with better WM performance [Hampson et al., 2006, Sala-Llonch et al., 2012]. Our finding of decreased connectivity between DLPFC and cingulate with development is consistent with cross-sectional studies showing decreased connectivity between cingulate and

DLPFC with development [Fair et al., 2007, Kelly et al., 2009]. Given parallel decreases of FEF connectivity through adolescence, the cingulate region may play a more cognitive role in WM compared to the mnemonic/sensory role of VAC. Activation in the anterior cingulate cortex has been found to underlie developmental improvements in inhibitory control in a longitudinal study through its role in performance monitoring [Ordaz et al., 2013]. In the present study, decreases in DLPFC/cingulate functional connectivity may reflect a decrease in the cognitive effort to generate a WM response.

A recent study places these findings in context [Sneve et al., 2013]. The authors examined adults perfoming a visual WM task, and used directed connectivity (Granger) analysis to show a hierarchy of WM processing regions. They found that the ventrolateral prefrontal cortex (VLPFC) influenced FEF and parietal activity during memory encoding; this is consistent with our finding of developmental change in DLPFC-FEF connectivity during encoding. Further, FEF predicted activity in regions of VAC during memory retrieval, consistent with our finding that protracted WM development in late adolescence and early adulthood is associated with DLPFC-VAC connectivity during retrieval. Together with this study, our findings suggest that the interaction of networks involved in executive and sensorimotor processing underlie mature WM performance. Next, we investigate a possible mechanism that may underlie developmental changes in connectivity and improvements in WM performance with age by investigating developmental changes in the integrity of structural white matter connectivity.

4.0 DEVELOPMENT OF STRUCTURAL CONNECTIVITY ASSOCIATED WITH WM DEVELOPMENT (DTI)

4.1 BACKGROUND

As we showed in the last chapter, there are changes in functional connectivity with adolescent development. This is consistent with findings that processes associated with connections among neurons, such as synaptic pruning, dendritic arborization, and myelination continue through adolescence and beyond, speeding the integration of neurons and supporting mature network function [Huttenlocher, 1990, Huttenlocher and Dabholkar, 1997, Pfefferbaum et al., 1994, Yakovlev and Lecours, 1967]. It also contrasts with measures like brain volume, weight, regional functional specialization, and cortical folding, which are largely comparable to adults by early childhood [Armstrong et al., 1995, Giedd et al., 1999, Reiss et al., 1996].

Histological studies have shown that most white matter matures early in development, including spinal roots and basic sensorimotor pathways [Yakovlev and Lecours, 1967]. In contrast, prolonged development occurs in frontal, parietal, and temporal white matter (WM) [Huttenlocher, 1990, Huttenlocher and Dabholkar, 1997, Yakovlev and Lecours, 1967], as well as connections to limbic regions such as the hippocampus [Benes et al., 1994]. Cross-sectional studies using diffusion tensor imaging (DTI), which provide in vivo measurements of WM integrity, generally find that the development of WM extends over childhood and adolescence, particularly in fronto-temporal and limbic connections, such as the uncinate fasciculus, superior longitudinal fasciculus and the cingulum, as well as cortical-subcortical connections involving the frontal lobes and motor regions [Asato et al., 2010, Barnea-Goraly et al., 2005, Giorgio et al., 2008, Lebel et al., 2008, Schmithorst et al., 2002, Tamnes et al., 2010].

To date, several two time point follow-up DTI studies of development have been published [Bava et al., 2010, Giorgio et al., 2010, Lebel and Beaulieu, 2011, Wang et al., 2012], all demonstrating ongoing development of white matter during adolescence. However, these studies were limited in several important ways including: small sample sizes, which limits the power to detect developmental effects, and comparisons of only two time points, which undermine the ability to characterize growth trajectories. Finally, prior studies have typically examined a narrow age span, limiting developmental inferences about the timing of white matter maturation. Cross-sectional studies have suggested that several white matter pathways have nonlinear growth patterns [Hermoye et al., 2006, Lebel et al., 2008, Lebel et al., 2012, Mukherjee et al., 2001], which may be mirrored by nonlinear growth in various motor and cognitive abilities [Kail, 1993, Luna et al., 2004]. These findings suggest the intriguing possibility that there may be qualitatively distinct changes in WM and behavior associated with different stages of development.

In our previous cross-sectional DTI study [Asato et al., 2010], we identified regions exhibiting adolescent-specific immaturities in white matter by comparing 1317 year-olds to 1830 year-olds. In the present longitudinal study, the primary aim was to use DTI methods to explore individual WM growth by including a large number of participants with three or more scans, and to use non-linear regression models in order to study the timing of regional/localized white matter maturation. We hypothesized a hierarchical maturation pattern first occurring in cortico-subcortical tracts, followed by cortico-cortical and corticolimbic tracts which would corresponds with the maturation of cognitive/behavioral performance.

4.2 METHODS

4.2.1 Study Population

As we are reporting on previously published results here [Simmonds et al., 2014], the sample is slightly different. Participants included 128 typically developing individuals (67 female) ages 8-29 years (mean age at start of study = 14.9 4.2). Each individual was scanned 1-5

times (1: 44, 2: 24, 3: 25, 4: 20, 5: 15) for a total of 322 scans. For individuals with multiple scans, successive scans were separated by a minimum of 6 months (interscan interval: 1.1 0.5 years).

4.2.2 DTI Acquisition

Scanner details were described in Aim 1. Diffusion images were obtained using a spin-echo echo-planar imaging sequence; whole-brain coverage was achieved using 29 4mm-thick contiguous axial slices with an in-plane resolution of 1.56mm. Similar to other developmental DTI studies [Barnea-Goraly et al., 2005, Schmithorst et al., 2002], diffusion gradients were applied in 6 non-collinear directions. However, in the present study directions were averaged over 14 repetitions (b = 800 s/mm) in order to increase the signal-to-noise ratio. A minimally-diffusion weighted image (b0) was also acquired. The axial plane was aligned with the anterior and posterior commissures to ensure consistency of image acquisition across subjects.

4.2.3 DTI Preprocessing

Data were initially processed using DTIPrep software [Liu et al., 2010] to automatically identify and correct motion and scanner-induced artifacts. These procedures included identifying slice intensity artifacts, in which motion reduces the correlation of neighboring slices within a gradient, and gradient intensity artifacts, in which motion leads to a large variance from other gradients; none were detected. Further, data were all visually inspected by the first author (DS) on a slice-by-slice basis during analysis to identify intensity artifacts including banding and poor signal-to-noise ratio; again, no artifacts were detected.

Data were then processed for analysis using the Oxford Centre fMRI of the brain Software Library (FSL) [Smith et al., 2004]. Raw DICOM images from the scanner were converted to NIFTI format using dcm2nii. Following this, a mask was created using brain extraction (bet) which segmented the brain from skull and other extracranial structures. Next, images were corrected for head motion and eddy current distortion (eddycorrect). Finally, a tensor model was fit to the images (dtifit), in which each voxel was assigned 3 eigenvectors and

eigenvalues, describing the water diffusion within the voxel. The standard measures of axial diffusivity (AD; diffusion along principal axis), radial diffusivity (RD; diffusion orthogonal to principal axis) and fractional anisotropy (FA; ratio of AD to RD, normalized on a scale from 0-1, with zero indicating isotropic diffusion and one indicating all diffusion in one direction) of each voxel were calculated for use in further analysis.

Additional processing for group analysis was performed using FSLs Tract-Based Spatial Statistics (TBSS) toolbox [Smith et al., 2006]. For each measure (FA, AD, RD), images were eroded by zeroing out voxels on the border of the image to reduce registration artifact, resampled to 1x1x1mm, and normalized to the JHU-DTI81 template included with FSL. An FA skeleton was generated, by calculating a mean FA map across subjects and thresholding it at FA>0.2. Individual subject skeletons were then normalized to the mean skeleton. For RD and AD measures, these images were registered to the FA skeleton.

In order to best understand the spatial patterns of development, region-of-interest (ROI) analyses were performed in successively smaller steps. In the first step, all voxels were averaged to create an overall white matter skeleton average. Next, the skeleton was divided into two groups of white matter; core tracts based on the JHU-DTI81 atlas [Mori et al., 2005] and white matter regions adjacent to gray matter, which we termed regional termination zones (RTZs), based on the Harvard-Oxford cortical and subcortical atlases provided with FSL. The JHU core tracts were divided into five categories: 1) callosal tracts, including splenium, body, genu and tapetum; 2) cerebellar tracts, including inferior, middle and superior cerebellar peduncles; 3) projection tracts, including medial lemniscus, pontine crossing tract, corticospinal tract, cerebral peduncle, posterior thalamic radiation, internal capsule (subdivided into anterior, posterior and retrolenticular portions) and corona radiata (subdivided into anterior, superior and posterior portions); 4) association tracts, including external capsule, sagittal stratum, superior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus; and 5) limbic tracts, including cingulum (subdivided into cingulate and hippocampal portions) and fornix (subdivided into column/body and crescent). Data were averaged over each category as well as averaged over the tracts within each category on an individual basis. The cortical RTZs included: frontal, sensorimotor, parietal, occipital and temporal. Subcortical RTZs included: cerebellum, basal ganglia, thalamus and medial

temporal. Further, as studies have shown significant differences in DTI measures between hemispheres [Wahl et al., 2010], we separated all ROIs into homologous left and right regions to look at hemispheric differences.

These regions are illustrated in Figure 19 and described in Table 4.

4.3 RESULTS

Results below are presented for developmental effects and hemispheric differences. For each model, average WM effects are first presented, followed by core WM categories, then individual tracts and RTZs. P-values are from omnibus chi-squared tests showing that a region has a significant main effect of or interaction with age. Ranges indicate the ages when growth or interactions are significant; multiple significant periods are separated by a forward slash.

4.3.1 White Matter Development

Developmental effects were evident across the brain, with all tracts reflecting increases in FA with age with no regions showing significant decreases (See Figure 20). FA averaged across the WM skeleton continued to grow into mid-adolescence (stages: 11.2-16.3, p=5.5e-06). In the core WM categories, projection tracts were mature by childhood (p=0.14), while other categories matured during adolescence, including callosal (stages: 11.9-15.4, p=0.0062), cerebellar (stages: 11.6-15.5, p=0.00046), limbic (stages: 11.5-16.5, p=5.1e-09) and association (stages: 8.2-16.7, p=4.4e-07).

Further, distinct trends in maturation were seen across individual tracts. Many tracts showed no effects of age indicating that maturation was complete by childhood; the majority of these tracts were middle and posterior projection tracts, connecting brainstem and subcortical regions to parietal and occipital cortex, including the medial lemniscus, pontine crossing tract, internal capsule (posterior and retrolenticular), corona radiata and posterior thalamic radiation. Additionally, portions of the interhemispheric corpus callosum (genu, body, tapetum) were mature in childhood, as well as the superior frontal occipital fasciculus,

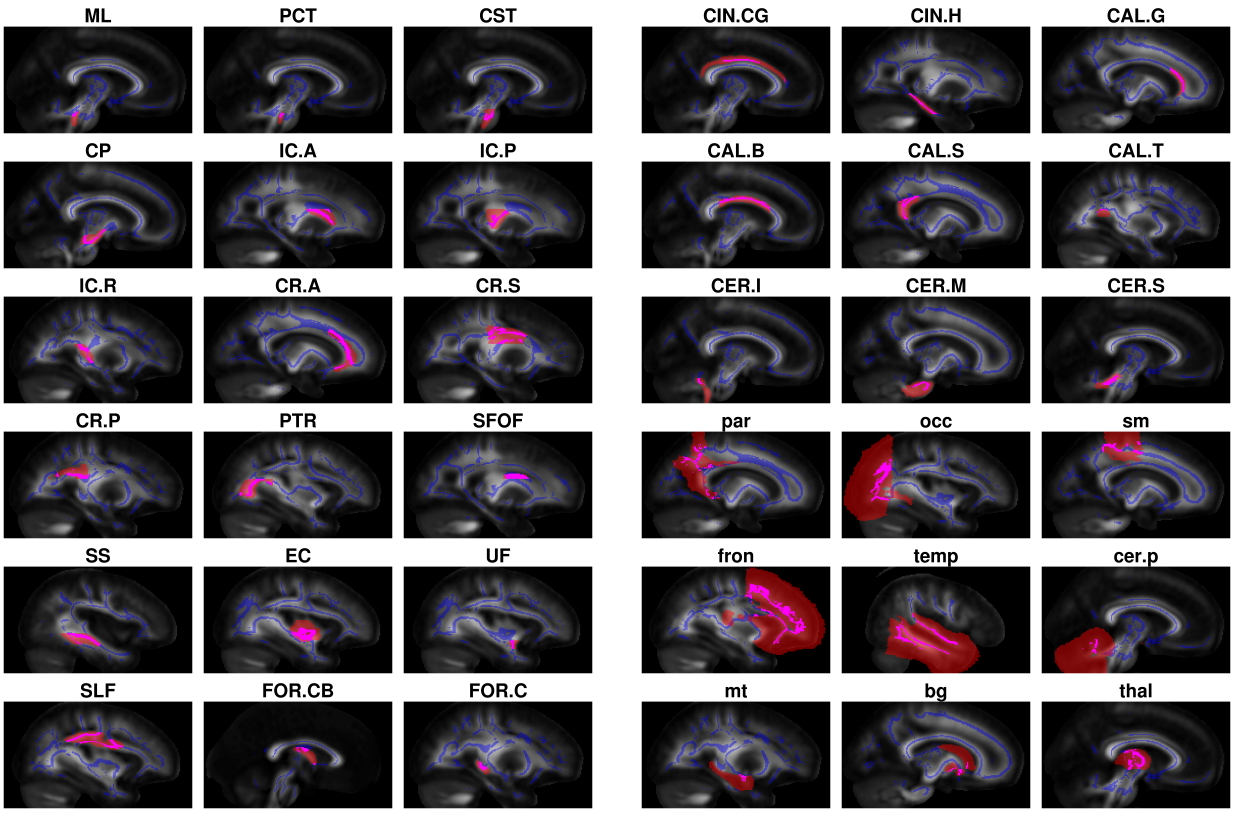


Figure 19: Sagittal slices showing ROIs used in analyses. Overlaid on an FA atlas, blue indicates the white matter skeleton, red shows the ROI, and their intersection in pink shows the voxels that are included in analysis. For each ROI, the slice with the largest number of intersection voxels was selected for display.

group	name	connection	abbreviation
	all WM average	all	all
core tract groups	projection	cortical - subcortical	proj
	association	cortical - cortical	assoc
	limbic	cortical - limbic	assoc.limb
	callosal	interhemispheric	cal
	cerebellar	cerebellar input/output	cer.c
projection tracts	medial lemniscus	spinal cord - brainstem	ML
	pontine crossing tract	spinal cord and cerebellar crossing fibers	PCT
	corticospinal tract (brainstem portion)	sensorimotor	CST
	cerebral peduncle	brainstem - internal capsule	CP
	internal capsule (anterior)	thalamus - frontal cortical	IC.A
	internal capsule (posterior)	corticospinal and thalamocortical	IC.P
	internal capsule (retrolenticular)	thalamus - posterior cortical	IC.R
	corona radiata (anterior)	internal capsule - cortical	CR.A
	corona radiata (superior)	internal capsule - cortical	CR.S
	corona radiata (posterior)	internal capsule - cortical	CR.P
	posterior thalamic radiation	optic radiation	PTR
association tracts	superior fronto-occipital fasciculus	frontal - parietal - occipital	SFOF
	sagittal stratum	frontal - occipital - temporal	SS
	external capsule	frontal - parietal - occipital - temporal	EC
	uncinate fasciculus	hippocampus - orbitofrontal cortex	UF
	superior longitudinal fasciculus	frontal - parietal - occipital - temporal	SLF
limbic tracts	fornix (column/body)	hippocampus - septal nuclei	FOR.CB
	fornix (crescent)	hippocampus - septal nuclei	FOR.C
	cingulum (cingulate portion)	hippocampus - parietal - frontal	CIN.CG
	cingulum (hippocampal portion)	hippocampus - parietal - frontal	CIN.H
callosal tracts	corpus callosum (genu)	interhemispheric frontal	CAL.G
	corpus callosum (body)	interhemispheric sensorimotor/posterior	CAL.B
	corpus callosum (splenium)	interhemispheric posterior	CAL.S
	corpus callosum (tapetum)	interhemispheric posterior	CAL.T
cerebellar tracts	cerebellar peduncle (inferior)	cerebellar input	CER.I
	cerebellar peduncle (middle)	cerebellar input	CER.M
	cerebellar peduncle (superior)	cerebellar output	CER.S
cortical RTZs	parietal		par
	occipital		occ
	sensorimotor		sm
	frontal		fron
	temporal		temp
subcortical RTZs	cerebellar		cer.p
	medial temporal		mt
	basal ganglia		bg
	thalamus		thal

Table 4: Description of ROIs included in analysis. Groups of ROIs identified are used for Holm corrections. A description of the ROI and abbreviations used in figures and tables are detailed as well. Shading is used as a visual aid to separate groups of ROIs.

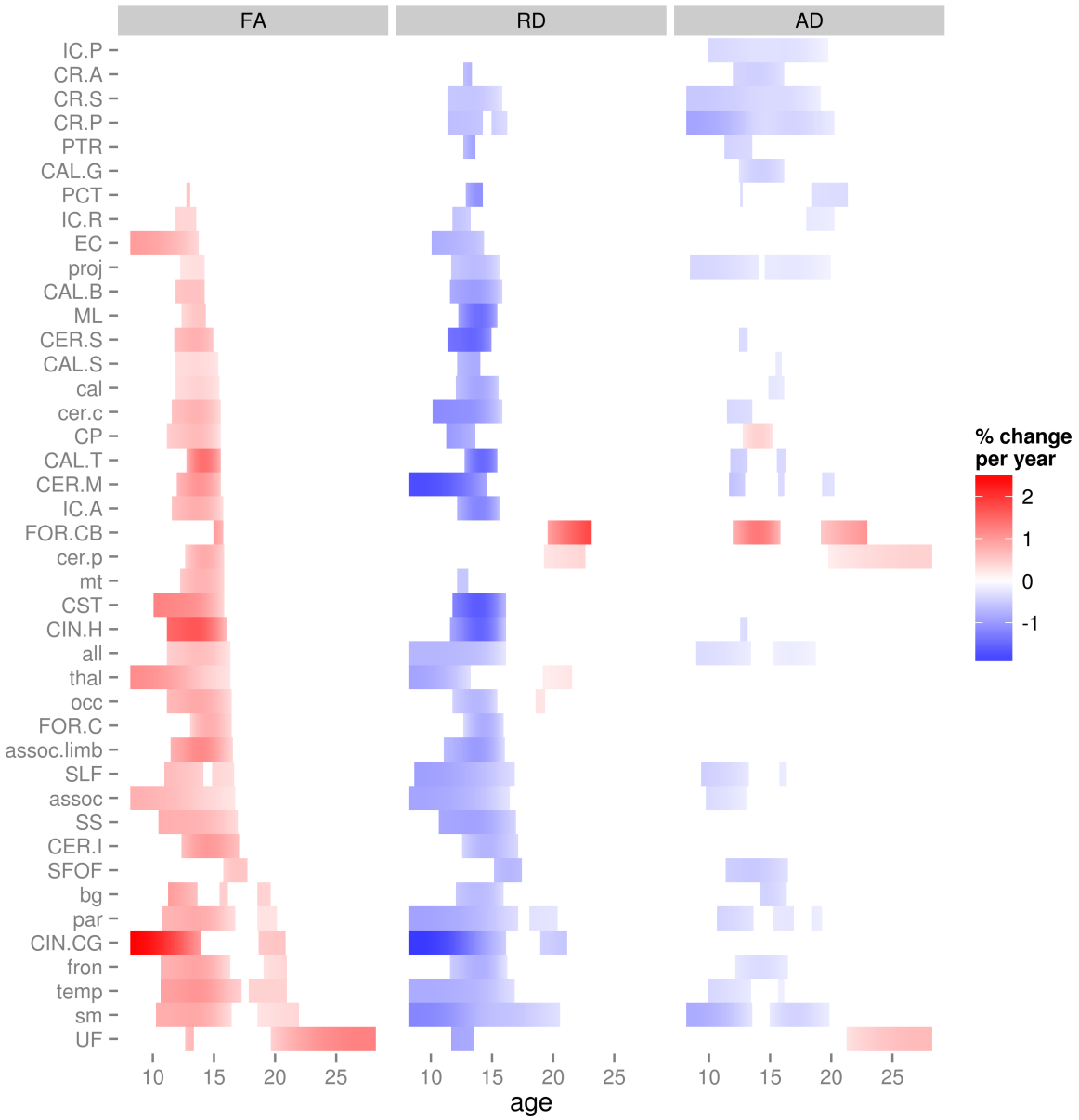


Figure 20: Stages of significant growth and timing of maturation in white matter development. Figure is divided into three columns corresponding to FA, RD and AD, respectively. Each row is an ROI whose label abbreviation is explained in Table 4; rows are sorted by time of maturation in FA, which is defined as the time that the rate of change was no longer significantly different from the null (p=0.05, bootstrap corrected). Colors represent % change per year (red = increasing, blue = decreasing).

(association tract connecting frontal, parietal and occipital regions), and the column/body portion of the fornix, (limbic tract connecting the septal nuclei to the hippocampus).

As indicated, the majority of white matter reached maturation during adolescence. Maturation during this time was seen for the remainder of the projection tracts, connecting brainstem and subcortical regions to frontal cortex, including the corticospinal tract (stages: 10.1-15.8, p=7.1e-07), cerebral peduncles (stages: 11.2-15.5, p=3.9e-05) and anterior internal capsule (stages: 11.6-15.7, p=7.6e-05). Also reaching maturation during adolescence were the interhemispheric callosal fibers, with the posterior splenium maturing last (stages: 11.9-15.3, p=0.0035), and all cerebellar white matter reached maturation during this time as well (superior stages: 11.8-14.9, p=0.0014; middle stages: 12-15.5, p=0.0039; inferior stages: 12.4-17, p=0.00013). Many long-distance cortico-cortical association tracts, including the sagittal stratum (stages: 10.5-16.9, p=1.2e-07), external capsule (stages: 8.2-13.7, p=7e-04) and superior longitudinal fasciculus (stages: 11-14.1 / 14.9-16.6, p=0.00024), as well as cortico-hippocampal limbic tracts, including the crescent portion of the fornix (stages: 13.1-16.4, p=0.0018) and the hippocampal portion of the cingulum (stages: 11.2-16, p=1.7e-06), reached maturation during adolescence as well. Finally, RTZs began to mature during this time; this included subcortical RTZs in the thalamus (stages: 8.2-16.3, p=1.1e-08), medial temporal lobes (stages: 12.3-15.8, p=0.0089) and cerebellum (stages: 12.7-15.8, p=0.044), as well as occipital cortical RTZs (stages: 11.2-16.4, p=9.3e-08).

After adolescence and into adulthood there was continued growth in major frontal and limbic tracts that reached maturity at different ages. Most RTZs showed growth into the second decade of life (frontal (stages: 10.7-16.3 / 19.1-20.9, p=4e-09), sensorimotor (stages: 10.3-16.4 / 18.6-21.9, p=4.9e-11), parietal (stages: 10.8-16.7 / 18.6-20.1, p=9.7e-10) and temporal (stages: 10.7-17.2 / 18.6-20.1, p=1.1e-13) cortical and basal ganglia (stages: 11.3-13.6 / 15.5-16.1 / 18.6-19.6, p=0.00011)). The cingulate portion of the cingulum (connecting frontal, parietal and hippocampal regions) (stages: 8.2-13.9 / 18.7-20.8, p=3.3e-07) matured during this time as well. The uncinate fasciculus (connecting the orbitofrontal cortex, amygdala, hippocampus, and medial temporal lobes) (stages: 12.7-13.3 / 19.7-28.2, p=0.0064) was the latest maturing region, with development continuing into the end of our sample age range (28.2 years). Further, it is notable that for all of these regions, there was an interim

period during adolescence with no significant growth.

No interaction of age and hemispheric differences were found in the WM average or core WM categories (all p>0.1). In individual tracts, interaction was seen in the cingulate portion of the cingulum (stages: 12.9-16, p=0.00022), tapetum (posterolateral) portion of the corpus callosum (stages: 15.6-17, p=5.1e-06) and basal ganglia RTZ (stages: 15.8-21.7, p=0.00012). These effects all reflected significant growth in the left hemisphere tracts (cingulum: p=0.00014, corpus callosum: p=0.028, basal ganglia: p=0.0087); during these periods, no significant growth was seen in these tracts in the right hemisphere.

4.3.2 Radial Diffusivity (RD) and Axial Diffusivity (AD)

RD decreases with development largely mirrored the FA findings described above (see Figure 20). RD averaged across the WM skeleton continued to grow into mid-adolescence (stages: 8.2-16.1, p=2.3e-07). All five WM categories matured during mid-adolescence, and the timing of tracts and RTZs were mostly similar to those in FA, with some notable differences. The uncinate fasciculus matured in early adolescence (stages: 11.7-13.5, p=0.001), while frontal (stages: 11.6-16.2, p=6.6e-06) and temporal (stages: 8.2-16.8, p=1.7e-13) cortical and basal ganglia (stages: 12.1-15.9, p=0.00011) RTZs matured during mid-adolescence. In contrast, the occipital (stages: 11.8-15.4 / 18.6-19.3, p=0.00073) and thalamic (stages: 8.2-13.2 / 19.2-21.5, p=0.0021) RTZs matured during early adulthood. Further, there were no significant interactions of age and laterality on RD.

In contrast with FA, AD typically decreases with development, and the timing of developmental change is mainly orthogonal to FA and RD findings (see Figure 20). AD averaged across the WM skeleton decreased into early adulthood (stages: 9-13.4 / 15.3-18.7, p=0.00014). In the WM categories, limbic and callosal tracts did not change over development (p>0.05), association (stages: 9.8-13, p=0.012) and cerebellar (stages: 11.5-13.5, p=8.4e-05) tracts matured in early adolescence, and projection (stages: 8.5-14 / 14.6-19.9, p=1.7e-07) tracts continued to decrease into adulthood. A majority of tracts and RTZs did not significantly change over development. Tracts showing decreases and maturing during adolescence include the posterior thalamic radiation (stages: 11.3-13.5, p=0.00036),

anterior corona radiata (stages: 12-16.1, p=0.00036), superior fronto-occipital fasciculus (stages: 11.4-16.4, p=7.3e-05), superior longitudinal fasciculus (stages: 9.4-13.2 / 15.8-16.3, p=0.0021), and frontal (stages: 12.1-16.4, p=0.0014), temporal (stages: 10-13.4 / 15.7-16.1, p=0.001) and basal ganglia (stages: 14.2-16.3, p=0.0094) RTZs. Tracts showing decreases and maturing in adulthood were mainly projection tracts, including pontine crossing tract (stages: 12.6-12.7 / 18.4-21.3, p=0.0016), posterior internal capsule (stages: 10-19.7, p=2.2e-09), superior corona radiata (stages: 8.2-19.1, p=1.9e-10) and posterior corona radiata (stages: 8.2-20.2, p=5.3e-14), as well as the middle cerebellar peduncle (stages: 11.7-12.9 / 15.7-16.1 / 19.3-20.2, p=8.9e-05). In contrast, the fornix (column/body) showed developmental increase in AD, maturing in adulthood (stages: 12-15.8 / 19.2-22.9, p=1e-04). The uncinate fasciculus also showed this pattern of developmental increase (stages: 21.3-28.2, p=0.04), although the region did not reach significance after Holm correction.

There were only a few significant interactions of age and hemisphere on AD. In posterior thalamic radiation during late childhood (stages: 12.2-12.5, p=0.00048), there was negative growth in the left hemisphere (p=5.4e-05), but not the right hemisphere (p=0.09). In the uncinate fasciculus during adolescence/early adulthood (stages: 15.3-20, p=1.4e-06), there was negative growth in the right hemisphere (p=0.0089), but not the left (p=0.28). In the fornix (column/body portion) throughout development (stages: 11.8-15.4 / 17.3-17.9 / 25-28.2, p=1.6e-05), there was positive growth in the left hemisphere in childhood/adolescence (p=2.37e-06) and adulthood (p=0.00632), but not in the right during any period (all p>0.05).

4.3.3 Behavior Interaction

As with the other aims, we examined correlations between DTI and behavior, focusing on FA. We narrowed our focus to white matter regions that connected our fMRI ROIs and showed protracted development through adolescence; further, we only examined right-lateralized ROIs to match up with the right prefrontal lateralization during WM. The regions examined for interactions were the cingulum, SLF, and SS (see Figure 21), as well as RTZs in frontal, temporal, parietal and occipital regions.

While all brain-behavior interactions with BOLD activity and connectivity were with

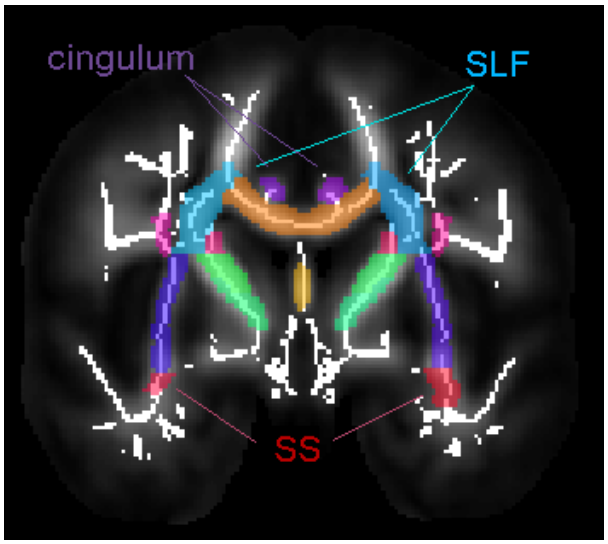


Figure 21: Association tracts examined for interactions with behavior and functional activity/connectivity. Overlaid on a coronal slice of the FA template, atlas regions are shown in color; annotated are the cingulum (purple), SLF (blue) and SS (red).

latency, brain-behavior interactions with FA were seen with precision. This finding is key because precision of the WM response is the measure that has previously been found to show protracted development. Associations were seen in occipital (p=0.0022) and parietal (p=0.00039) RTZs. In both occipital (8.1-14.1) and parietal (8.1-12.2) RTZs, association was seen in childhood and early adolescence such that faster growth in FA was associated with more precise responding (see Figure 22). Further, late developmental association was seen in occipital RTZ (17.6-28.2), such that growth in FA during this time was associated with less precise responding.

4.3.4 Association with BOLD

Finally, we examined associations between FA and DLPFC BOLD activity/connectivity, to see whether these developmental changes depend on the development of anatomical connections. We first looked at association between DLPFC maintenance activity and FA, finding that higher FA in parietal (p=0.0024; stages=8.1-19.2) and occipital (p=0.039; stages=8.1-

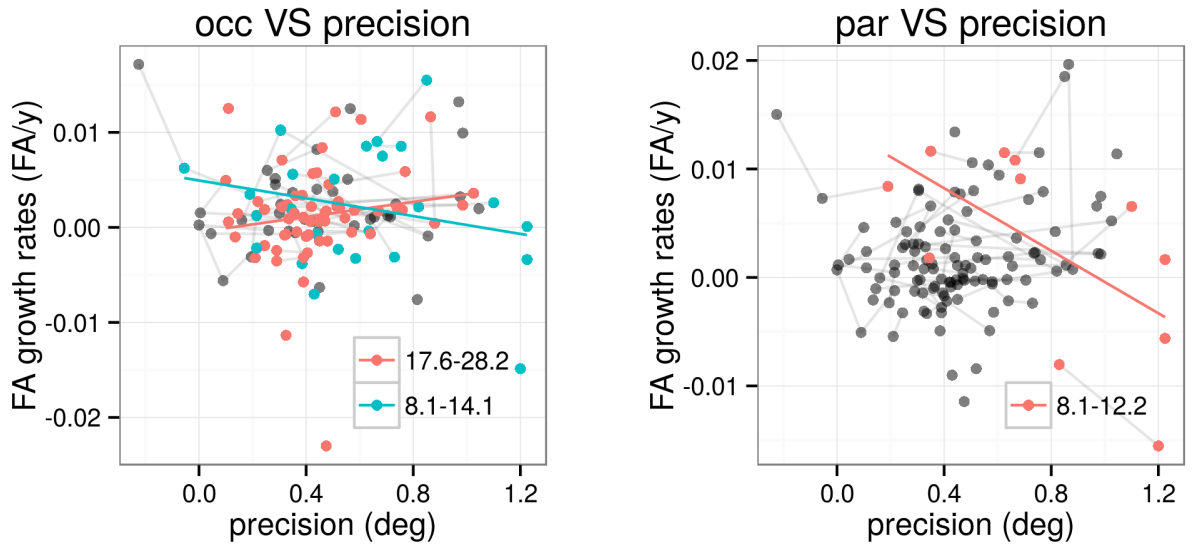


Figure 22: Brain-behavior association between FA in occipital (left) and parietal (right) RTZs and precision. Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored, as labeled in the legend within each plot. The colored lines indicate interactions within each stage. In childhood and early adolescence, there was a negative correlation between FA growth rates and precision, such that greater developmental increases in FA were associated with more precise responding. In late adolescence and adulthood, there was a positive correlation between FA growth rates and precision, such that greater developmental increases in FA were associated with less precise responding.

18) RTZs was associated with higher DLPFC growth rates during childhood and adolescence (see Figure 23).

All of the association tracts examined, as well as occipital RTZ, showed correlations with BOLD connectivity, with distinct association patterns. The cingulum was specifically associated with connectivity between DLPFC and anterior cingulate during encoding (p=0.0036; stages=8.1-14.6, 18.9-28.2) and maintenance (p=0.0039. stages=17.9-28.2) (see Figure 24).

The SLF (p=0.0022; stages=8.1-15.1, 18.8-28.3), SS (p=7.8e-08; stages=8.1-16.1, 18.8-28.2), and occipital RTZ (p=0.0028; stages=8.1-15.6, 19.1-28.2) were all associated with connectivity during encoding between DLPFC and VAC (R fusiform/inferior temporal, BA20/37) (see Figure 25). As with the cingulum, higher FA was associated with higher BOLD connectivity growth rates in childhood, and lower rates in adulthood.

4.4 DISCUSSION

4.4.1 White Matter Development

To date, studies of brain changes associated with white matter development have largely relied on cross-sectional designs, whether examining development of BOLD activity [Geier et al., 2009, Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007, Scherf et al., 2006], BOLD connectivity [Dosenbach et al., 2010, Fair et al., 2007, Hwang et al., 2010] or DTI white matter integrity [Asato et al., 2010, Barnea-Goraly et al., 2005, Giorgio et al., 2008, Lebel et al., 2008, Schmithorst et al., 2002, Tamnes et al., 2010]. Some studies have used repeated measures follow-up with two time points [Bava et al., 2010, Darki and Klingberg, 2014, Giorgio et al., 2010, Lebel and Beaulieu, 2011, Ullman et al., 2014, Wang et al., 2012], limiting the ability to characterize growth trajectories and make direct inferences about developmental change. The present study included up to five annual data points for each subject, allowing us to apply mixed-effects regression to understand the timing and stages of white matter development, which has not previously been examined.

Results showed that for several late-maturing regions including those connected to pre-

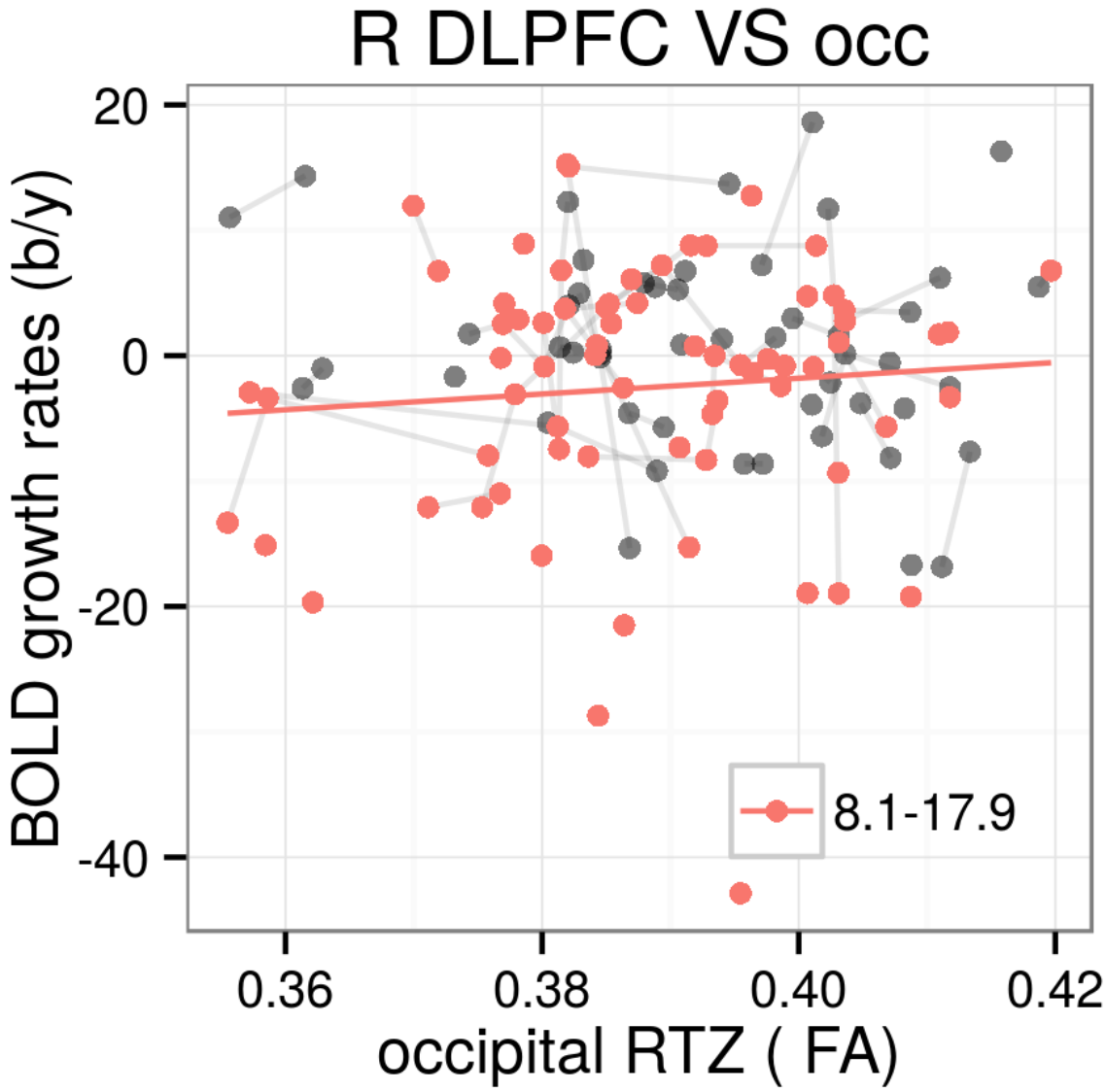


Figure 23: Function-structure developmental relationship between FA in occipital RTZ and development of DLPFC maintenance activity. Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored, as labeled in the legend within each plot. The colored lines indicate interaction within the stage. Although DLPFC maintenance activity did not significantly change with developent across the group, individual differences in the development of its activity were still related to white matter differences.

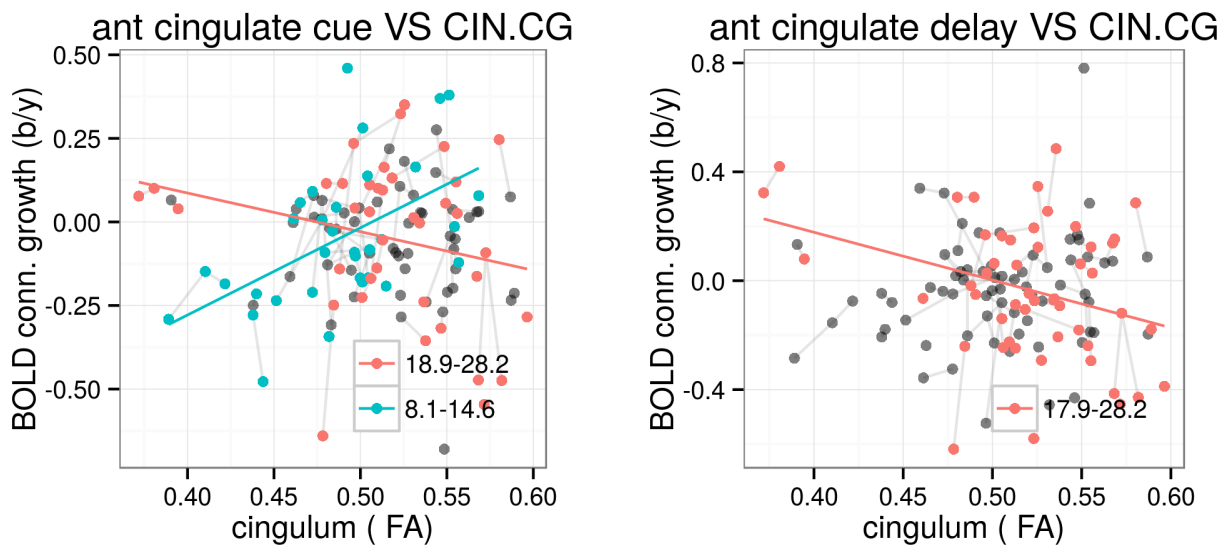


Figure 24: Function-structure developmental relationship between FA in the cingulum and development of DLPFC-anterior cingulate connectivity during encoding and maintenance. Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored, as labeled in the legend within each plot. The colored lines indicate interaction within the stage.

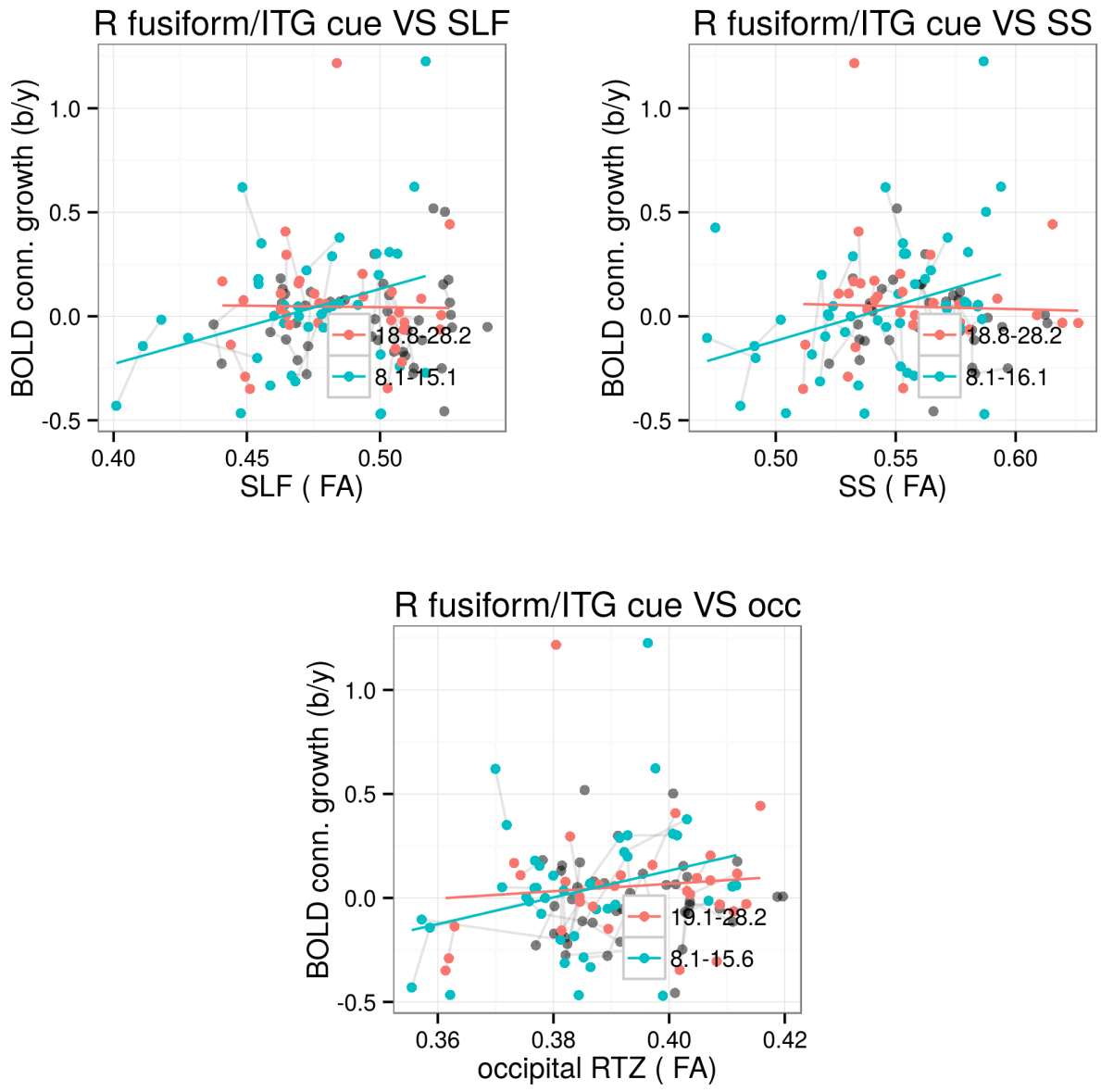


Figure 25: Function-structure relationship between development of DLPFC-VAC connectivity during encoding and FA in the SLF (top left), SS (top right), and occipital RTZs (bottom). Raw smoothed growth rates are shown in gray, with points in the same individual connected by lines; points corresponding to the interaction stage are colored, as labeled in the legend within each plot. The colored lines indicate interaction within the stage.

frontal regions, distinct phases of growth were seen, with rapid growth in childhood, followed by a slowdown slowing of growth in early-middle adolescence and acceleration of growth again in late adolescence/early adulthood. This is consistent with postmortem studies in prefrontal cortex showing a late adolescent spurt of growth in synaptic density [Huttenlocher, 1990, Paus et al., 2008]. While discrete growth periods have been observed for in young children with EEG coherence [Thatcher, 1992], this is the first longitudinal identification of such stages during the adolescent period in white matter maturation. This finding is key, as most studies only investigate simple linear, inverse or quadratic models of development and cannot identify discrete periods of white matter development.

Topographically, results showed that many projection tracts integrating posterior cortical and subcortical structures to brain stem regions were largely mature by late childhood, whereas frontocortical and frontosubcortical connections grew through adolescence maturing approximately by 15-16 years of age. Growth continued into adulthood the second decade of life in major corticolimbic association tracts and regional termination zones (RTZs) in cortical and basal ganglia regions. Overall, these results agree with findings from cross-sectional and follow-up DTI studies [Asato et al., 2010, Barnea-Goraly et al., 2005, Bava et al., 2010, Giorgio et al., 2008, Giorgio et al., 2010, Lebel et al., 2008, Lebel and Beaulieu, 2011, Schmithorst et al., 2002, Tamnes et al., 2010, Wang et al., 2012]. However, the present study extends these findings, allowing the detection of discrete periods of significant growth with interim periods of decreased growth.

Of the regions that were already mature in childhood, many play a role in basic sensorimotor function. The posterior thalamic radiation carries visual sensory information from the retina to the primary visual cortex via the thalamus, while portions of the internal capsule and corona radiata carry somatosensory information from the spinal cord and brainstem to the primary sensory cortex via the thalamus [Mori et al., 2005, Schmahmann and Pandya, 2006]. These findings are consistent with the early maturation of basic sensorimotor function seen in prior studies [Luna et al., 2004], which is critical to support the later development of cognitive functions.

Many of the regions that mature in adolescence play a pivotal role in motor response preparation and executive function. For example, the superior longitudinal fasciculus con-

nects frontal and parietal regions important for motor planning and initiation, spatial attention, working memory and language [Dosenbach et al., 2007, Sauseng et al., 2005, Schmahmann and Pandya, 2006, Schmahmann et al., 2007, Vincent et al., 2008]. These findings are consistent with studies showing that executive and cognitive functions including response inhibition and working memory continue to mature into adolescence, when adult-level performance is reached [Bedard et al., 2002, Luna et al., 2004, Williams et al., 1999].

Growth in cortical and basal ganglia RTZs continued into adulthood. These results agree with post-mortem analysis of myelination has demonstrated studies showing a prolonged maturation of intracortical white matter [Yakovlev and Lecours, 1967]. Specifically, we found that occipital based tracts matured in adolescence, while other cortical regions mature in adulthood, consistent with evidence of a posterior to anterior hierarchy in maturation of synaptic density and myelination [Huttenlocher, 1990, Petanjek et al., 2011, Yakovlev and Lecours, 1967]. Further, late maturation was also seen in the basal ganglia, which forms loops with the cortex and is a key relay in cognitive and emotional processing [Middleton and Strick, 2000]. Late maturation of these areas may suggest that a large cortical-subcortical network is critical for integrating cognition and emotion.

Further, growth of the uncinate fasciculus and cingulum also continues into the second decade of life. Both of these tracts link orbital and medial prefrontal cortical regions to medial temporal regions, with the cingulum functioning as a dorsal limbic pathway, and the uncinate as a ventral limbic pathway [Mori et al., 2005, Schmahmann et al., 2007]. The cingulum connects hippocampal regions to the cingulate, with fibers extending to DLPFC [Mori et al., 2005, Schmahmann et al., 2007]. The hippocampus and surrounding areas are important for memory function [Mishkin, 1982, Squire and Zola-Morgan, 1991] which have been found to develop past childhood [Ghetti and Bunge, 2012]. The DLPFC is involved in WM and staying on task [Gazzaley and Nobre, 2012, Ikkai and Curtis, 2011] and shows differential activity supporting cognitive performance in development [Luna et al., 2010]. Further, both these regions show protracted development of synaptic density and myelination [Benes et al., 1994, Huttenlocher and Dabholkar, 1997], supporting their role in the development of cognition through adolescence [Luna et al., 2004]. The cingulate cortex is situated between these regions in the circuit. Functional imaging studies demonstrate that the anterior cingulate is

involved in both error and reward processing [Walton et al., 2007] and activation associated with these is still immature in adolescence [Eshel et al., 2007, Fjell et al., 2012, Velanova et al., 2008]; hence, it may contribute to the development of the link between cognition and emotion through adolescence. Although not discussed in this thesis, this conclusion is supported by our finding of developmental brain-behavior correlation in the cingulum with inhibitory performance [Simmonds et al., 2014].

Whereas the cingulum reached maturation early in the third decade, growth continued throughout our sampled age range in the uncinate fasciculus, late into the third decade. Most of the regions with significant developmental change showed increases in FA and decreases in RD, thus likely related to greater myelination; in contrast, developmental change in the uncinate fasciculus during adulthood was related to increases in FA and increases in AD, more consistent with greater axonal density. Similarly protracted development has been described in the equivalent tract in adolescent rats, specifically related to fiber density [Cunningham et al., 2002]. The uncinate fasciculus connects the orbitofrontal cortex to the amygdala and hippocampus, as well as superior and inferior temporal regions [Schmahmann et al., 2007]. The orbitofrontal cortex is important for reward processing and decision making [O'Doherty et al., 2003], and is particularly relevant for the development of social behaviors, which show dramatic change in adolescence [Blakemore and Robbins, 2012, Paus et al., 2008]. Lesions of the orbitofrontal cortex in adolescent monkeys leads to decreased anxious and fearful behaviors [Kalin et al., 2007] and inability to adjust to social situations [Eslinger et al., 2004]. In humans, activation in orbitofrontal cortex is reported in functional imaging studies of social cooperation/competition tasks [Hampton et al., 2008, McCabe et al., 2001] and is associated with risk-taking behaviors [Chein et al., 2011, Shad et al., 2011]. The uncinate is also connected to the anterior temporal lobes, which has been shown to play a critical role in representing and retrieving social knowledge [Olson et al., 2012], as well as the amygdala, which is important for emotional development [Tottenham, 2012]. Further, connectivity in this tract is abnormal in psychiatric populations; adolescents with disruptive behavioral disorders have decreased functional connectivity between orbitofrontal cortex and amygdala [Marsh et al., 2011], and depressed patients have lower FA in the uncinate [Versace et al., 2010]. Hence, the uncinate is a critical mediator between cognitive and emotional processing,

and may be a significant factor in the pathophysiology of adolescent psychopathology.

Consistent with prior studies developmental DTI studies, both AD and RD decreased with development. Furthermore, developmental increases in FA reflect that RD decreases to a greater extent than AD [Wang et al., 2012]. RD changes largely mirrored those of FA, suggesting that the majority of the developmental changes in FA are related to myelination [Song et al., 2002, Song et al., 2005]. Since AD changes were predominantly decreases, AD increases in the cingulum and uncinate fasciculus during early adulthood are notable and suggest that these limbic changes may be more related to increased axonal density [Cunningham et al., 2002, Song et al., 2002].

In sum, these results suggest a hierarchical maturation of WM where basic sensorimotor and brain stem systems mature first followed by executive systems through adolescence while tracts that support integration of executive and emotion systems continue to mature into adulthood.

4.4.2 Brain-Behavior and Structure-Function Associations

We found that posterior BOLD was associated with precision in posterior RTZ white matter. This is important because while WM is available in infancy [Diamond et al., 1994], what has been previously shown to continue to improve through adolescence is the precision of WM responses [Luna et al., 2004]. This finding suggests that protracted developmental changes in WM precision may be specifically related to having a structural scaffold in place for connections to posterior cortical regions.

Typically, studies have found associations between BOLD and WM performance in association tracts, such as the SLF and the cingulum [Charlton et al., 2010, Golestani et al., 2014]; however, most studies look only at whole tracts or core white matter bundles, rather than looking at intra-lobular RTZs. While in Aims 1 and 2, we found that DLPFC activity was associated with behavior in childhood/early adolescence, and DLPFC/VAC connectivity was associated with behavior in late adolescence/early adulthood, posterior FA was associated with behavior during both periods. This suggests that developmental changes in white matter may be linked to both processes, consistent with previous studies finding associa-

tions between DTI and both BOLD activity [Burzynska et al., 2013, Olesen et al., 2003] and connectivity [Fair et al., 2008, Honey et al., 2009] measures.

Associations between FA and BOLD measures confirm this; FA in occipital RTZs was linked both to DLPFC BOLD activity during maintenance and DLPFC connectivity with posterior regions during encoding and maintenance. Further associations between functional connectivity and FA were seen in all 3 association tracts examined (cingulum, SLF, SS), and these tracts were specifically associated with functional connectivity in regions they connect, consistent with findings that structure and function show a joint maturation [Olesen et al., 2003]. Taken together, these findings indicate that underlying age related improvements in WM performance from childhood through adulthood, as well as specialization of WM-related activity and connectivity, is the development of the structural integrity of white matter connections, specifically those within or connecting to VAC.

5.0 GENERAL DISCUSSION

5.1 SUMMARY & CONCLUSIONS

In this study, we characterized how the development of local brain functional *specificity* (activity), functional *integration* (connectivity), and structural *connectivity* support the development of working memory (WM) from childhood to adulthood. Importantly, this is the first longitudinal study combining functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) with more than two time points to investigate longitudinal trajectories of working memory.

We confirmed that WM performance improved with age showing asymptotic growth through adolescence [Luna et al., 2004] that continued into the third decade of life. Specifically, correct WM responses were evident throughout all ages but the precision of the saccade to the remembered location improved and its latency continued to decrease into the twenties. That is, WM is much advanced by childhood hence changes in brain processes are to be understood in their ability to support improvements in speed and precision of a response, not the basic ability to generate a WM-guided response. This protracted developmental time course is especially notable as the Memory-Guided Saccade (MGS) task does not have extra cognitive demands known to be developmentally sensitive, such as needing to remember additional items [Thomason et al., 2009], performing operations on the contents of WM [Crone et al., 2006], or resilience in the face of distractors [Olesen et al., 2007]. The MGS task is distinct from prototypical tasks that require manipulation of information during the delay period [Baddeley, 1992] in that it taps specifically on the delay dependent neural processes that underlie the ability to retain a representation on-line [Chelune and Baer, 1986, Luna et al., 2004].

Just as children are capable of the basic ability to generate a WM response, the canonical regions involved in WM are active across all ages. These regions include but are not limited to the dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF), and visual association cortex (VAC) [Owen et al., 2005, Rottschy et al., 2012]. Primary findings across study aims in these regions are summarized in Table 5, with a pictorial representation in Figure 26.

While most developmental WM studies have focused on age related changes in DLPFC processing finding mixed results [Geier et al., 2009, Klingberg et al., 2002, Kwon et al., 2002, Olesen et al., 2007, Scherf et al., 2006], we found that it was engaged at similar levels across ages, consistent with evidence that DLPFC is recruited similarly in adolescents and adults in cognitive control [Ordaz et al., 2013]. Due to our use of the MGS task, it is evident that the DLPFC is involved in visuospatial WM maintenance even in the absence of extra cognitive demands. Further, we found that greater DLPFC recruitment was associated with slower responding, reflecting its role in supporting executive and not mnemonic processes, such as sensory gating [Postle, 2005]; more specifically, DLPFC can perform the mnemonic role, but may be less specialized than other regions of the WM circuitry for MGS performance. This suggests that core DLPFC executive processes involved in maintenance may be available by childhood, supporting correct WM performance. However, while a similar canonical WM circuitry including DLPFC, FEF and VAC is engaged across all ages, key developmental changes were found in regions connected to DLPFC, supporting incremental refinements in WM (see Figure 26).

The fact that there is a widely-distributed circuitry that supports WM underscores the importance of connectivity. During encoding of a visual stimulus strong connectivity between DLPFC and VAC would support a timely precise executive visual response. As indicated previously, there is growing evidence that VAC supports the representation of information to be remembered in working memory [D'Esposito and Postle, 2015, Riggall and Postle, 2012, Sreenivasan et al., 2014a, Sreenivasan et al., 2014b]. Neural circuitry in visual cortex may provide a refined spatial map that supports mnemonic processing underlying the level of precision seen in adult WM performance. Our results showed that in adulthood DLPFC/VAC connectivity was present across encoding, maintenance, and retrieval periods of the MGS task as well as the incorporation of the FEF that support executive motor con-

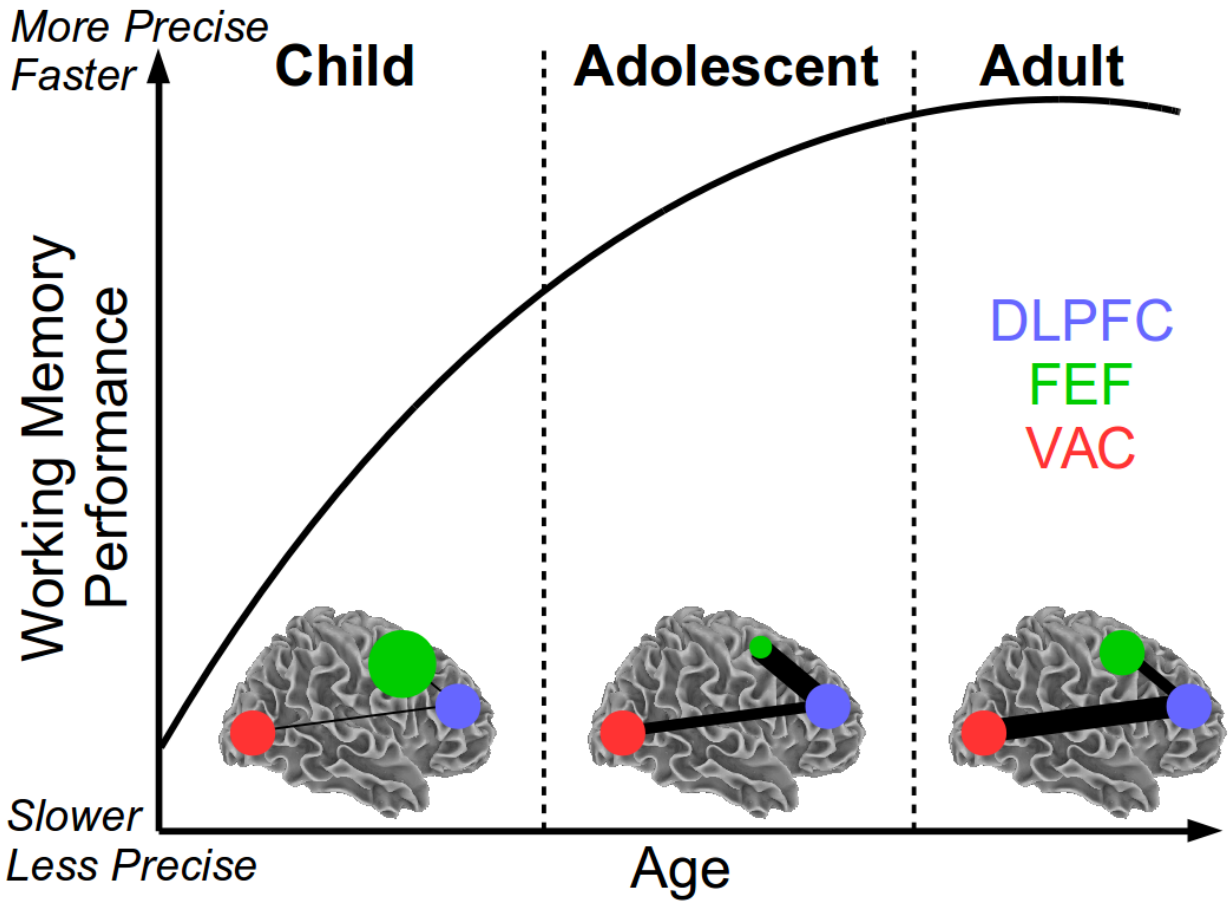


Figure 26: Representation of primary findings across study aims, highlighting developmental change in Dorsolateral Prefrontal Cortex (DLPFC; blue), Frontal Eye Fields (FEF; green) and Visual Association Cortex (VAC; red). The size of the circles represent the magnitude of activity in each region, and the thickness of the lines represents the strength of connectivity between the regions. The underlying lineplot shows faster and more precise responding with age, with larger gains in childhood and smaller gains in adolescence.

	DLPFC	**FEF**	**VAC**
1) Functional Specificity	Engaged similarly across age during maintenance	Engaged during maintenance with U-shaped trajectory *decreasing* into adolescence, *increasing* into early adulthood	
Association w/Behavior	BOLD *decreases* with *faster* latencies	BOLD *increases* with *faster* latencies in childhood & adolescence	
2) Functional Integration with DLPFC		Encoding U-shaped trajectory, *increase* into adolescence, *decrease* into early adulthood	All epochs, *increase* into early adulthood
Association w/Behavior			*Less* connectivity associated with *shorter* latencies in adulthood
3) Structural Connectivity Association	*Less* FA in occipital & parietal RTZs was associated with BOLD *increases* during maintenance in childhood & adolescence		*Greater* FA in SLF & SS was associated with connectivity *increases* during encoding in childhood & adolescence but during adulthood *less* FA was associated with connectivity *increases*

Table 5: Summary of primary findings across study aims, organized by region.

trol providing a model for mature optimal brain systems supporting MGS performance to characterize development.

Initially, children appear to show levels of DLPFC/VAC connectivity lower than those of adults, instead relying on activation of FEF during maintenance at higher levels than teens and adults. The FEF is well understood to play a critical role in the control of eye movements [Munoz and Everling, 2004, Schall et al., 2002] with greater engagement when the control is generated endogenously such as in the MGS task [Curtis et al., 2004, Postle et al., 2000]. Teens engage DLPFC/VAC circuitry at greater levels than children but still lower than adults, as well as relying on DLPFC/FEF connectivity for encoding, while requiring less activity during maintenance in FEF. These findings may indicate a transitional period in adolescence as it starts to approximate adult levels, similar to behavioral findings in MGS performance. By adulthood, FEF activity and connectivity reaches intermediary levels of engagement, as mature VAC connectivity is reached. These results suggest that the transition to adulthood may reflect refinements of regional processing afforded by the engagement of optimally specialized processing in VAC. The importance of FEF and VAC and their developmental trajectory in WM is specifically supported by their association with WM latency, which occurs across development for FEF but is limited to adulthood for VAC, again highlighting how transitional states are critical before reaching mature WM.

Critically, white matter development supported these developmental changes in brain and behavior. Earlier maturation of white matter in posterior cortical Regional Terminal Zones (RTZs) was specifically associated with greater WM precision and increases in DLPFC-VAC connectivity during adolescence. On the other hand, poorer MGS performance in childhood was underlied by greater executive DLPFC involvement. Together, these results suggest that early in development the limited access to specialized posterior regions, due to still maturing white matter connectivity, may engage executive systems to perform the task. As long-distance association white matter tracts mature, speeding neuronal transmission and increasing fidelity of information processing, this would enhance DLPFC/VAC communication assisting visuospatial WM.

5.2 LIMITATIONS

5.2.1 Working Memory vs. Sustained Motor Processing

An important point of consideration is defining what aspects of working memory the MGS task probes. Specifically, the MGS task requires that only a single stimulus location be retained in WM with no distractors or manipulation. The lack of manipulation of the maintained information during the delay period could be interpreted as lacking the "working" part of WM [Baddeley, 1992] instead only engaging basic mnemonic processing and/or sustained motor preparation. Given, the known developmental improvements in inhibitory control and its engagement during WM manipulation, we purposely wanted to isolate the ability to retain information. We were particularly interested in the development of brain processes that support sustaining information on line to guide behavior. Our finding of protracted development in both measurements of WM performance into the early 20s suggests that even basic mnemonic processes alone are important in development. Our variant of the MGS task, required subjects to perform a VGS to the target compared to the typical MGS task that requires that fixation be retained and visual attention to code the visuospatial information to be retained in WM. This approach was chosen for two reasons. First, previous behavioral studies show that regardless of the duration of the delay period there is an equal difference in accuracy across age [Luna et al., 2004] suggesting that there may be limitation in encoding as well as maintenance. Hence, providing ample ability to encode with a VGS provided an approach to control for encoding differences. Second, inhibitory control continues to improve through adolescence [Ordaz et al., 2013] resulting in more dropped trials in younger participants when using the traditional MGS that requires that fixation be maintained during the presentation of the to be remembered stimulus. This specific manipulation allowed us to assess developmental changes in optimal encoding circumstances to better understand developmental changes in the ability to guide behavior based on the information retained in WM.

5.2.2 Assessing Independent Activation of Task Epochs

A further key strength of the study is that we modeled task epochs separately to quantify developmental changes specific to encoding, maintenance and retrieval. We used an event-related design with jittered inter-trial intervals and different lengths for encoding and maintenance epochs, which helped reduce collinearity between epochs. However, we did not use a partial (catch) trial design that further reduces collinearity; further, for half the trials, delay length (1.5s) did not exceed hemodynamic lag times. Because of this, it is possible that developmental findings specific to an epoch may include activity bleeding over from adjacent epochs. The optimal solution would be to use a design incorporating either catch trials or longer delay periods. However, one solution that can be employed in the current dataset is to do a time-course model of the data that does not assume an apriori hemodynamic shape [Geier et al., 2009]; while this does not allow specific separation of epoch-related activity, it prevents activity from one epoch being assigned to another.

5.2.3 Selection of Regions of Interest (ROIs) in study

Another important consideration is that, due to the high power of the study, we were able to use a separate sample of subjects to define the regions to avoid any issues of circularity. However, we chose to examine regions showing age effects in the cross-sectional sample to focus our longitudinal analyses, that may have undermined our ability to capture all developmental changes. One approach would have been to define ROIs from the adult sample; however, we avoided this approach as it might unfairly bias our results towards finding a developmental effect. A more encompassing approach is to define ROIs based on regions that showed a main effect of time across ages and use these to investigate age effects using the longitudinal data. This will be done for the manuscript.

5.2.4 Regional Terminal Zones (RTZs) and the Tensor Model

In our study, we found a link between posterior cortical RTZs and behavior, as well as functional specificity and integration. An important caveat to this white matter association

is that unlike in the major tracts, like the superior longitudinal SLF or cingulum, the tensor model does not hold well in RTZs due to many crossing fibers [Schmahmann et al., 2007], limiting interpretability to histological measures like myelination; newer diffusion acquisitions with a greater number of directions are needed to obtain more accurate measures in these regions [Yeh et al., 2013].

5.3 CONCLUSIONS & FUTURE DIRECTIONS

Working memory precision continues to improve through adolescence in parallel with brain maturational processes of systems that support the integration of executive and sensorimotor processes. By utilizing a large longitudinal study design and studying individual differences in development, we were able to show that these developmental changes across brain and behavior were intricately linked. Protracted developmental changes in executive and sensorimotor processes both contributed to late maturation of WM. In the absence of additional cognitive demands, integration of sensorimotor processes may play a primary role in age related improvements in WM precision, while persistent reliance on executive processes may reflect suboptimal immature processing. Importantly, we found that development was not a linear process but that the adolescent period reflected a stage of re-organizing predominance by different regions in supporting WM perhaps afforded by enhancements on structural connectivity supporting the integration of key regions. Hence, early in development MGS performance is more difficult and is led by executive processes, next in adolescence connectivity is strengthened to integrate sensory regions, by adulthood there seems to be a stable circuitry that engages posterior regions that support a fast and accurate MGS.

One next step from these findings would be to test for developmental differences in the ability to decode accuracy based on the multivariate pattern across voxels of the VAC as done with adults [Riggall and Postle, 2012, Sneve et al., 2015, Sreenivasan et al., 2014a, Sreenivasan et al., 2014b]. In this manner, we could find more direct evidence that integration of this sensory region in fact does support greater MGS accuracy with age. This method would be the next important step in the study; due to findings in adults that precision of

the WM response is associated with the degree to which stimuli can be decoded from VAC [Sreenivasan et al., 2014a, Sneve et al., 2015], we hypothesize that decoding accuracy would improve with development.

Another next step of great significance is to characterize abnormal developmental trajectories. Adolescence is a period when psychopathology can emerge including schizophrenia and mood disorders [Kessler RC et al., 2005, Paus et al., 2008], which are characterized by impaired WM [Paus et al., 2008]. The evidence of a prolonged development of the precision of WM may reflect an extended period of plasticity during the adolescent period that may mirror the specialization of brain maturation to its particular environment reflecting both vulnerabilities for abnormal development such as in psychopathology, but also opportunities in acquiring adult level complex cognitive processing. Given this extensive characterization of normal brain development underlying WM, it will be important to examine it in populations with abnormal development. However, delineating normal developmental brain changes in this period is a key step in understanding the brain basis of these disorders.

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[Chafee and Goldman-Rakic, 1998] Chafee, M. V. and Goldman-Rakic, P. S. (1998). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working MemoryTask. *Journal of Neurophysiology*, 79(6):2919–2940. Chafee, Matthew V. and Patricia S. Goldman-Rakic. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J. Neurophysiol. 79: 2919–2940, 1998. Single-unit recording studies of posterior parietal neurons have indicated a similarity of neuronal activation to that observed in the dorsolateral prefrontal cortex in relation to performance of delayed saccade tasks. A key issue addressed in the present study is whether the different classes of neuronal activity observed in these tasks are encountered more frequently in one or the other area or otherwise exhibit region-specific properties. The present study is the first to directly compare these patterns of neuronal activity by alternately recording from parietal area 7ip and prefrontal area 8a, under the identical behavioral conditions, within the same hemisphere of two monkeys performing an oculomotor delayed response task. The firing rate of 222 posterior parietal and 235 prefrontal neurons significantly changed during the cue, delay, and/or saccade periods of the task. Neuronal responses in the two areas could be distinguished only by subtle differences in their incidence and timing. Thus neurons responding to the cue appeared earliest and were more frequent among the task-related neurons within parietal cortex, whereas neurons exhibiting delay-period activity accounted for a larger proportion of task-related neurons in prefrontal cortex. Otherwise, the task-related neuronal activities were remarkably similar. Cue period activity in prefrontal and parietal cortex exhibited

comparable spatial tuning and temporal duration characteristics, taking the form of phasic, tonic, or combined phasic/tonic excitation in both cortical populations. Neurons in both cortical areas exhibited sustained activity during the delay period with nearly identical spatial tuning. The various patterns of delay-period activity—tonic, increasing or decreasing, alone or in combination with greater activation during cue and/or saccade periods—likewise were distributed to both cortical areas. Finally, similarities in the two populations extended to the proportion and spatial tuning of presaccadic and postsaccadic neuronal activity occurring in relation to the memory-guided saccade. The present findings support and extend evidence for a faithful duplication of receptive field properties and virtually every other dimension of task-related activity observed when parietal and prefrontal cortex are recruited to a common task. This striking similarity attests to the principal that information shared by a prefrontal region and a sensory association area with which it is connected is domain specific and not subject to hierarchical elaboration, as is evident at earlier stages of visuospatial processing.

[Chafee and Goldman-Rakic, 2000] Chafee, M. V. and Goldman-Rakic, P. S. (2000). Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *Journal of Neurophysiology*, 83(3):1550–1566. Dorsolateral prefrontal and posterior parietal cortex share reciprocal projections. They also share nearly identical patterns of neuronal activation during performance of memory-guided saccades. To test the hypothesis that the reciprocal projections between parietal and prefrontal neurons may entrain their parallel activation, the present experiments have combined cortical cooling in one cortical area with single-unit recording in the other to more precisely determine the physiological interactions between the two during working memory performance. The activity of 105 cortical neurons during the performance of an oculomotor delayed response (ODR) task (43 parietal neurons during prefrontal cooling, 62 prefrontal neurons during parietal cooling) was compared across two blocks of trials collected while the distant cortical area either was maintained at normal body temperature or cooled. The mean firing rates of 71% of the prefrontal neurons during ODR performance changed significantly when parietal cortex was cooled. Prefrontal neurons the activity of which was modulated during the cue, delay, or saccade periods of the task were equally vulnerable to parietal inactivation. Further, both lower and higher firing rates relative to the precool period were seen with comparable frequency. Similar results were obtained from the converse experiment, in which the mean firing rates of 76% of the parietal neurons were significantly different while prefrontal cortex was cooled, specifically in those task epochs when the activity of each neuron was modulated during ODR performance. These effects again were seen equally in all epochs of the ODR task in the form of augmented or suppressed activity. Significant effects on the latency of neuronal activation during cue and saccade periods of the task were absent irrespective of the area cooled. Cooling was associated in some cases with a shift in the best direction of Gaussian tuning functions fit to neuronal activity, and these shifts were on average larger during parietal than prefrontal cooling. In view of the parallel between the similarity in activity patterns previously reported and the largely symmetrical cooling effects presently obtained, the data suggest that prefrontal and parietal neurons achieve matched activation during ODR performance through a symmetrical exchange of neuronal signals between them; in both cortical areas, neurons activated

during the cue, delay, and also saccade epochs of the ODR task participate in reciprocal neurotransmission; and the output of each cortical area produces a mixture of excitatory and inhibitory drives within its target.

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